AN HISTORICAL AND CRITICAL STUDY OF

URAEMIA.

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BY

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C O N T E N T S.

INTRODUCTION.

It is 82 years since Piorry, a French physician, first used the term "uraemia," although the symptoms and associated retention of urea had been observed much earlier. Since that time the true significance of the word has changed, and uraemia has come to include a great variety of symptoms met with in Renal Diseases. The comprehensive nature of the term, at first a convenience, has, by the multiplicity of the manifestations included, become unwieldy. Ever since the association of certain symptoms with renal insufficiency their investigation has been one of the most popular fields of research and speculation. A very great amount of work has been done, and our knowledge of the state of the body when giving rise to uraemic symptoms is now great. From the etiological point of view, however, the value of much of the work has been mainly of a negative nature - that of disproving the various suggestions -, and in spite of the large accumulation of facts during more than one hundred years, the cause of the condition is still unknown.

Before commencing the Thesis proper, I propose briefly to explain why this subject was selected, and also to indicate its aims and scope. I first became especially interested in the subject of uraemia when studying Renal Disease with a view to making a speciality of this branch of medicine. I was struck by the unsatisfactory nature of the descriptions of

uraemia in the text-books and systems of medicine. My interest being aroused I endeavoured to obtain as much of the literature that I could, both of this country and abroad, having a bearing upon the subject. The amount of literature is enormous, and yet I was unable to find any book on "uraemia." It all exists as short isolated articles dealing with the results of experiments, observations of clinical phenomena, etc., and short descriptions which only indicate a few of the main facts of the subject, but nowhere could I find a serious comprehensive attempt to correlate these various clinical, pathological and biochemical findings.

There have been great advances recently, notably in the sphere of biochemistry, but most of the work has been done on the Continent or in America, and little has been done of recent years in this country, and although in the larger text-books and systems of medicine short scattered references are made to recent suggestions, yet the general descriptions and theories of the etiology of uraemia are much the same as they were twenty years ago. Anyone interested in the subject, therefore, has to expend a large amount of time and labour in collecting and reading the relevant literature before becoming acquainted with the subject as a whole. I felt that it would be of valuable

assistance to have in one volume a complete description of the condition, and of the work and conclusions of investigators in all spheres. To collect all these isolated data and put them into orderly form is my first aim.

The value of such a collective review of the work done from the beginning is to help one to formulate a clearer idea of the probable etiology of the condition. There has been a great deal of new ground explored in recent years, but much of the work done awaits correlation. Many of the older theories require reconsidering in the light of recent researches, and the modern ones await criticism. My second aim, therefore, is to describe fully and discuss these theories, and, by so doing, to clarify our conception of the condition, and to narrow and indicate the path along which future research is most likely to prove productive. In this Thesis I do not suggest a new theory. I hesitate to do this for two reasons. First, because the subject is so vast that I do not believe the solution of the problem will be the work of one man, but that, as almost certainly in the cancer problem, it will be evolved from the work of many, and also because I agree with those who believe that uraemic symptoms are not all caused by the same factor, but that there may be several different causes. Secondly, because I think that there are already too many existing theories, and that these

should be carefully considered and finally rejected or retained before any new theory is advanced which, by adding to those already existing and awaiting acceptance, would only increase the present confusion and difficulties. These additional considerations induce me to believe that a book containing a description of the various researches and opinions of the many workers would prove helpful. A great deal of research in the past has been conducted upon illogical lines. Theories formed and the facts made to fit the theories, instead of theories fitting the facts. For example, whilst it was natural to associate urea with the condition after the discovery of the increase of the blood urea, the next logical step should have been to ascertain if urea is toxic and if so to assume it the cause, and not to make the assumption first and investigate the toxicity of urea afterwards. While, therefore, I do not propose to put forward a new theory, and the Thesis is mainly a critical survey of the work done on the subject, yet original suggestions which may prove helpful in the solution of the main problem are made in the appropriate places.

There is no need to stress the clinical importance of uraemia. This is apparent when one remembers that it has been estimated that at least 40

per cent, of patients suffering from obvious renal diseases die with these symptoms. Also, the manifestations of uraemia are so diverse that often the true nature of the condition is not realised until some more characteristic phenomena occur. A better understanding of the condition will, therefore, lead to earlier diagnosis, and while this does not necessarily mean that it will be cured, yet it is reasonable to expect that by instituting a régime suitable for the underlying cause life will be prolonged. Recent advances in blood chemistry and in methods of estimating the efficiency of the kidneys have been of very great value both for earlier diagnosis, and to enable us to study the condition. The importance of biochemical researches in uraemia cannot be too strongly emphasised. Eclampsia and uraemia have often been coupled together on account of the sometimes almost identical clinical pictures, and the similarities in pathology. In this case, however, the clinical appearance can be very misleading, for the blood chemistry, principally of the products of nitrogenous metabolism, is strikingly different; the marked retention which is a feature of uraemia being absent in eclampsia. This does not mean of course that the two conditions may not have the same cause, but it does suggest that the retention of those substances which differ in the two conditions does not

cause the symptoms of uraemia. I do not propose to include a description of eclampsia in this Thesis though much of the subject matter is applicable to both, but where a comparison may be helpful this is made.

The scope of any thesis to achieve the ends I have indicated must be wide, and I therefore propose to deal with the subject under the following headings:-

PART I. HISTORICAL. This part includes an account of the more important points in the history of the condition, and also a description of the older theories, which are fully described and discussed in order to leave one free to deal with only the more modern ones later.

PART II. SYMPTOMATOLOGY:- A full description of the clinical phenomena. There is a marked diversity of opinion as to what symptoms may be justifiably termed "uraemia," and there is a growing tendency to the opinion that it is unjustifiable to describe uraemia as an entity at all. In the past the term was originally used because of the misconception that the retention of urea accounted for certain symptoms occurring with diseased kidneys. When urea was proved to be non-toxic, the name was retained as a convenient, comprehensive term for many symptoms of toxaemia which occur in several forms of renal disease or with any interference with the ordinary eliminative function of the kidneys. They are, in

the main, functional disorders of the nervous system, but also simulate diseases of other systems, principally the respiratory and digestive. The retention of the name "uraemia" is therefore quite wrong, its original significance having passed. The need for the retention of some such comprehensive term was largely due to the lack of knowledge and a satisfactory classification of renal diseases. Of recent years there has been a great increase in our knowledge of these diseases, and the classifications of Volhard and Fahr and of O'Hare render it unnecessary to describe uraemia as an entity, the various uraemic symptoms being included as parts of the clinical phenomena of the diseases with which they occur. I agree with those who think that there is no need to describe uraemia, as at present conceived, as a separate entity, and that the term "uraemia" should be dropped and the symptoms described under the headings of the diseases. With modern methods of diagnosis and tests of renal function these diseases should not be missed, and so the need for diagnosing "uraemia" should not arise. If the term "uraemia" is done away with, what is to become of the so-called "latent Uraemia?" Much of the difficulty in the past has been in trying to reconcile theories of uraemia with the clinical manifestations of latent uraemia. The

use of this term is also bad, and it too should be dropped. The endeavour to associate the two conditions so closely seems unreasonable for they are not comparable on clinical, pathological or etiological grounds. If one does away with this term, however, one must suggest another to take its place. In this condition the clinical picture is very definite and constant. It is a pure retention, and the symptoms can be described exactly, apart from others due to associated disease. It is necessary, therefore, to have a term for that group of symptoms due to retention in the blood, on account of the cessation of function of the kidneys, of the products which they normally excrete. "Anuria" alone is not satisfactory for this. It has its place in indicating lack of urine from any cause, which may be only temporary, and relieved before the typical symptoms appear. I would therefore suggest for this syndrome "A-nephrexia" - a state of non-functioning of the kidneys.

With regard to the conditions with which symptoms of uraemia may occur, these may be any diseases in which the kidneys are either diseased, or their function is impaired. As, for example, in cholera, in which the viscosity of the blood is the primary factor. In all these conditions the kidneys are not non-functioning as in "anephrexia," but partially functioning. For this state I would suggest the term "Dys-nephrexia"

So-called uraemic symptoms will therefore occur in any state of "dysnephrexia;" they may be slight or they may be severe, the difference being only one of degree, while "dysnephrexia" will occur with any condition in which the renal function is impaired, not necessarily primarily renal, but in such diseases as cholera, yellow fever or the late stages of cardiac disease, in which uraemic symptoms have been described.

The symptoms resulting from true retention in "anephrexia," and partial disability in "dysnephrexia" should be kept apart, and no attempt should be made, as has been done, to ascribe them to a common cause. In most conditions of "dysnephrexia" some degree of retention exists. If one takes the syndrome of "anephrexia" as indicating the symptoms of retention, one must subtract these from the clinical picture of "dysnephrexia" and there remain symptoms which must be due solely to the disease with which they occur, and are not necessarily renal in origin. These are really the only symptoms which may justifiably be described as "uraemic." I would emphasise once more, however, that I do not think there is any need to describe any symptoms as uraemic, and although I suggest the term "anephrexia" to replace "latent uraemia" I am not suggesting that "dysnephrexia" should rep-

lace "uraemia," but should only be used to mean impairment of or interference with the functioning of the kidneys, and it would obviously not include cases of disease of one kidney in which the other was satisfactorily performing the eliminative needs of the body.

In my description of the symptomatology in this part of the Thesis, I have endeavoured to give as many as possible of the manifestations of uraemia, and have partially retained the old classification for convenience.

PART III. PATHOLOGY AND BIOCHEMISTRY. In this part I have given, as fully as possible, an account of the pathological and biochemical changes associated with uraemia, with particular attention to the latest researches. It is in this branch that advance has been most rapid recently, as for example, the work of Folin and Wu which has greatly facilitated our investigation of the biochemistry of the blood and other fluids, and of Canti, who has done valuable work on the cerebro-spinal fluid etc. I have divided this part into the following sections:-

1. The Changes in the Organs in "Uraemia." (Kidneys, Suprarenal glands, etc.).
2. The Blood Chemistry in "Uraemia."
3. The Changes in the Urine in "Uraemia."

4. Changes in other Secretions and Excretions in "Uraemia." (Sweat, Saliva, Cerebro-spinal fluid etc.).

5. Recent Observations not referable to any of the Previous Sections. (e.g., Hermannsdorfer's experimental uraemia in rats in parabiosis).

PART IV. MODERN THEORIES OF THE ETIOLOGY. In this part the manifestations of uraemia are first carefully considered and correlated with the circumstances under which they occur, and a conception of uraemia is formulated. The more modern theories of the etiology are then described and discussed, and the effects upon them of the most recent researches indicated.

In conclusion, I have recapitulated the main opinions expressed in the course of the Thesis.

PART I.

A Summary of the Main Points in the History of the Study of the Etiology of Uraemia; with a Criticism of the Earlier Theories.

The history of uraemia may truly be said to commence with the observations of Richard Bright on Dropsy associated with certain pathological changes in the kidneys and the presence of albumin in the urine. It was thus possible to divide dropsy into the two great groups, Renal and Cardiac, permitting many of the symptoms previously described under "dropsy" to be referred to renal disease, and stimulating investigation of diseases of the kidneys. The symptoms later classified as "uraemia" were known, however, before Bright's observations.

The first important chemical investigations of the urine date from the time of van Helmont, who in 1644 isolated the solids of the urine and found among them common salt. He also ascertained the higher specific gravity of febrile urine, and discovered uric acid and calcium phosphate.[1] In 1773 Rouelle discovered urea,[2] the substance which has played such a an important part in the study of uraemia; it received its name from Fourcroy and Vauquelin in 1799.[3]

In their earliest days the symptoms of uraemia were known as the "head symptoms of dropsy." At that time dropsy was described as a separate entity; the earliest indication that there was more than one type occurring in 1776, when William Withering first

tried foxglove for the treatment of dropsy. He found that it proved unsuccessful in a certain proportion of cases, and there can be no doubt that many of these were cases of chronic nephritis.

Whilst the association of these "head symptoms" with renal disease was not known, yet it was known that urea was increased in the blood in many cases. In 1822 animal experiments were performed by Prévost and Dumas[4] to prove the association of the presence of urea with the inflammatory lesions, such as peritonitis, pericarditis, pleurisy and cellulitis, not infrequently exhibited by dropsical patients who had died with head symptoms. These experiments confirmed the belief in the connection between the two states, as the animals often showed similar lesions; but this was doubtless due to the fact that, as at that time the conception of aseptic operation had not been formulated, the conditions found when the animals succumbed with these curious manifestations were really those of bacterial infection.

In 1827 Richard Bright published his epoch making observations in his "Reports of Medical Cases," containing his original description of essential nephritis, and the distinction between cardiac and renal dropsy. Previous to this Wells in 1811[5] and Blackall in 1813[6] had established the correlation

between dropsy and albuminous urine, and even as early as 1476 Saliceto, an Italian surgeon, had pointed out the association of dropsy, scanty urine, and hardened kidneys,[7] but Bright was the first to connect these symptoms with the peculiar inflammation of the kidneys which he had found at so many post-mortems. The importance of his observations from the point of view of this Thesis, is that it permitted the "head symptoms," previously described as common with dropsy, to be definitely associated with disease of the kidneys, and very soon a classification was made into acute and chronic nephritis.

Chemical investigations were similarly greatly encouraged, and these centred chiefly round the albumin and urea. It was soon observed, by Solon in France, and by Christison in this country that the specific gravity of the urine was often low, in spite of the presence of albumin, and that this was due to a diminution of the urea and saline matters.[8]

At this time the significance of the increase of urea in the blood in certain dropsical cases, which, as has been described, was known much earlier, appears to have been quite overlooked. There would seem to have been no attempt at investigation of the blood chemistry. Urea was being investigated in the laboratory however, and in 1828 was synthesized from ammonium cyanate by Friedrich Wohler of Escher-

heim.[9]

Solon and others attempted to explain the association of albumin in the urine with a diminished excretion of urea by supposing the albumin to be formed at the expense of urea by a "sort of conversion."[10] Investigations at this time were chiefly concerned with albumin, and it was natural that this should produce the first theory put forward to explain the symptoms later called "uraemia." It was suggested that these symptoms were caused by hydraemia of the blood due to decrease of its albumin and pigments, it having been shown by Gooch and Marshall Hall that such a state was apt to be associated with stupor and coma.[11]

The theory that albuminuria was due to a vicarious excretion of urea was soon discredited, and in 1830 Christison observed that in the majority of cases when the urine was deprived of the greater part of its urea the amount of albumin was small, and vice versa.[12] This observation led to more careful investigation of urea and the blood, and was borne out by the remarkable fact that coincident with the presence of albumin in the urine urea could be found in the blood, where in health it could not be detected. The investigations of the changes in the state of the blood were mainly the work of

Christison, Babington and Barlow, and their results may be summarised as follows:- (1) Urea is often present in the blood but only when decreased in the urine. (2) The serum is apt to be of low specific gravity. (3) The proportion of fibrin varies. (4) The colouring matter decreases as the disease progresses.[13] Experimentally, urea was found in the blood of animals with extirpated kidneys, and in the liquids effused into the ventricles of the brain, pericardium, pleura and peritoneum. This led an observer in 1833 to ascribe the occurrence of fits and sudden death in connection with alleged disease of the kidneys, to alterations in the blood directly resulting from the kidney disease. Some of his actual words were as follows:- "The exact change of the blood may require further investigation, but the presence of urea and the deficiency of albumin are those which hitherto attracted the notice of Dr. Prout and Dr. Bright."[14]

In 1837 Osborne, in a treatise on "The Nature and Treatment of Dropsical Diseases," made the second attempt to explain the symptoms.[15] It had previously been noticed that the onset of brain symptoms was usually preceded by a diminution in the quantity of the urine, followed by coma, and finally by convulsions. Osborne's theory was that, "when a case has terminated in this manner, serum is sometimes

found accumulated in unnatural measure in the cerebral ventricles, and in the tissue of the pia mater. The dropsy has extended to the brain .... its presence and pressure may fairly be assumed to have produced the fatal symptoms." This theory of oedema of the brain and the earlier one of hydraemia were to be developed later by Traube in association with raised arterial pressure to produce his celebrated "mechanical theory."

Osborne's theory appears never to have been accepted, for many observers immediately described cases in which the urine became diminished but the brain was unaffected. There was also frequently no marked collection of water within the skull, and no appreciable changes; and sometimes no dropsy of any part of the body.

These facts, associated with the usual failure in quantity of the urine, and the presence of urea in the blood and even in the natural serum of the brain, led to the construction of the first important theory which was to hold its own for many years. This theory, which first became generally popular about 1840, assumed the toxicity of urea, and referred the "ultimate symptoms, the stupor, and the death, to the poisonous influence of the urea of the unpurified blood upon the brain and nervous system."[16].

About this time, Christison recorded a case in which the urine diminished markedly, no more than 2 oz. of light urine being passed daily for 9 days. The patient remained sensible to the last and died of inanition.[17] This is the first record of "obstructive anuria." As up to that time a reduction in the urine volume had been considered a preliminary to "head symptoms" this case attracted notice and is referred to by Watson, who, in his lectures in 1840, after describing renal dropsy, and with reference to the evolving theory of urea toxicity makes the following comment: "This theory, cannot yet be regarded as fully proved, ... Dr. Christison's observations are even calculated to throw a strong doubt upon its soundness."[18] Bright also recorded a case which lived 4 or 5 days, and had no fits until the end.[19]

This period is also interesting on account of the fact that Pierre Francois Olive Rayer of Calvados, who had already done a great deal of valuable work on the subject of renal dropsy, published his large three volume treatise on "Diseases of the Kidney, with Atlas" (1837-41),[20] the first recorded attempt in the literature to deal with the subject separately.

By this time the complications described as "head symptoms" - headache, drowsiness, delirium, epileptic seizures, had been noted so frequently by all observers that Christison considered them "the

natural termination of the disease, if not cut short by incidental disease."[21].

The urea theory had not yet (1840) become widely accepted, and it was considered that many of the symptoms were not due directly to the kidney disease, but to local and peculiar agencies. This impression arose on account of the prevalence of the symptoms differing in different places. Thus, the vomiting and diarrhoea were very commonly reported by the Edinburgh physicians and rare elsewhere, whilst the headache and coma so frequently described by the British physicians were, according to Solon, rarely seen in France.[22]

The theory that retained urea caused the symptoms by its toxic action was not the suggestion of any one individual. It slowly evolved by a process of elimination. As has been indicated, the earlier chemical investigations had centred round albumin. Owing to the theory that the presence of albumin in the urine with diminished excretion of urea was due to vicarious excretion of urea, the importance of urea as a potential factor in the production of the symptoms was lost sight of temporarily. This theory was disproved when urea was rediscovered in the blood. This startling fact, together with the overwhelming evidence against the suggested causes of the "head symptoms," stimulated enthusiasm in its investigation, and it gradually came to be

considered the dominant factor in the etiology.

The theory was a fascinating one. It was the first of the chemical theories. Chemical pathology was in its infancy. Physicians had come to regard the symptoms as a "poisoning of the system." No other possible poison could be demonstrated, at least in such large amount, and its presence was almost constant. One of the greatest factors that contributed to make its acceptance widespread, was the difficulty of disproving it. It is true that most observers were able to record cases in which head symptoms occurred without urea being found to be increased in the blood to any great extent, and vice versa; yet, by making reservations it was possible to make the theory generally acceptable. Due, therefore, partly to the difficulty of disproving it, and further because of the lack of a more feasible suggestion, the retention of urea came to be regarded as the most important factor in the causation of the symptoms, though other factors were admitted as likely to play a part. Thus, local conditions, as already mentioned, were still deemed important. It was known too that other constituents which were decreased in the urine must be retained in the blood, but the methods of chemical analysis were inadequate to demonstrate them. Later, however, as

these substances were isolated and their properties investigated, each one in turn, came to be considered the toxic factor.

Although the theory of urea retention became so universally popular, it seems never to have been generally accepted 'in toto,' and it is really the commencement of the later "Retention Theory" in which the symptoms were attributed to the combined action of all the normal ingredients of the urine. The important role assigned to urea was quite unwarranted by the evidence at that time. The same arguments which brought about the rejection of the earlier theories were equally applicable to this one, whilst the experiments on animals which had been carried out could be used equally well to prove as to disprove the suggestion, for in many cases they failed to produce any of the typical symptoms. In spite of these facts, however, for the next few years urea was the axis around which most of the discussion revolved, and this culminated in 1847 when Pierre Adolphe Piorry, a physician of Poitiers, first employed the term "Uraemia,"[23] to indicate a series of toxic symptoms, mainly nervous, associated with a retention of urea in the blood; and this term became universally accepted.

I cannot regard the introduction of this term as having assisted in the study of the condition.

It caused the subject to be described as a separate entity, and gave a definite descriptive name to an unknown condition. Even after the retention theory was dropped in its turn, the term "uraemia" was retained and so fixed urea in the minds of investigators that for many years almost all investigations centred round it. Whilst this undoubtedly produced most valuable and essential data, yet the name tended to prevent later investigators from approaching the subject with an open mind.

In 1850, Dr. Owen Rees of London in a work entitled, "On the Nature and Treatment of Diseases of the Kidney connected with Albuminous Urine," summarised the clinical objections to the urea theory. They were, briefly, that the occurrence and the severity of the uraemic symptoms did not necessarily bear relation to the quantity of urine, and that the blood was sometimes loaded with urea without any symptoms appearing. He attempted to revive the hydraemia theory and conceived that a "certain thin and watery state of the blood" was an essential condition for its production.[24] This was old ground however, and as uraemia occurred in many cases in which the blood was not watery, and watery blood was not always attended by uraemia, his view was not accepted.

Similar objections to the urea theory were put forward by Friedrich Theodor von Frerichs, a German physician who published a book in 1851 on "Die Bright'sche Nierenkrankheit," in which he propounded a theory which formed the next great landmark in the investigation of the subject.[25] Frerichs suggested that the toxic agent was not urea, but ammonium carbonate which was formed in the blood by the decomposition of urea. He maintained that this changes was brought about by a ferment, and very ingeniously explained those cases with increased blood urea but without uraemic symptoms, by assuming that urea might accumulate for long in the blood of patients affected with Bright's disease, but would not lead to any injurious influence unless a ferment were introduced. He sought to prove this view by showing that injection of carbonate of ammonia led to such symptoms, and that carbonate of ammonia was present in the blood of uraemic patients. He also claimed that he could demonstrate the presence of ammonia in the expired air of uraemic patients by holding a glass rod moistened with hydrochloric acid near the mouth, when white fumes of chloride of ammonia were formed, and by showing that moistened red litmus paper turned blue when held to the mouth. These observations were confirmed by many observers. Demjanikow observed uraemic phenomena after nephro-

tomy, when at the same time he injected the urea-ferment into the blood.[26] Dr. Petroff of Dorpat wrote an elaborate memoir supporting Frerichs' view.[27]

The originality and ingenuity of this theory caused it to become very popular, especially in Germany. During the succeeding years "ammoniaemia," as it came to be called, received marked attention. A modification of Frerichs' original idea was introduced by Treitz in 1859 and by von Jaksch senior, who amended the hypothesis by suggesting that the carbonate of ammonia was produced, not in the blood, but in the stomach and intestine; a vicarious excretion of urea into the alimentary canal first taking place, and subsequently carbonate of ammonia being absorbed.[28] This theory although often challenged, was adhered to by many for a long time.

In 1861 however, Oppler had made another suggestion.[29] He discredited the "ammoniaemia" theory because he found that the symptoms resulting from the injection of carbonate of ammonia were by no means identical with those seen in uraemia, and able chemists had failed to discover the salt in the blood of the uraemic. He found that there is a retention of the products of muscle waste in cases of Bright's disease, and conceived that there might be a similar retention of the products of nerve waste, and to the deleterious effects of this subs-

tance he attributed the symptoms.

Oppler's suggestion appears to have aroused very little interest. It was rather overshadowed by a new theory which had been put forward just previously by Ludwig Traube in Germany.[30] A theory which was to become very widely popular and which has existed in a modified form to this day.

Traube revived the older suggestions of cerebral anaemia and oedema and by combining these with the raised state of arterial tension so commonly noticed, produced the most important "Mechanical theory." He maintained that - as in Bright's disease, the blood serum being in an impoverished state, tends to transude, and in consequence of hypertrophy of the heart, the blood pressure in the arterial system is increased, - so, when from any cause this blood pressure is suddenly increased, or the density of the blood serum is further diminished, serous fluid transudes through the smaller arteries, and oedema of the brain results. As a result, the capillaries and veins are compressed, and the brain becomes correspondingly anaemic. The form of the attacks varies according to the part of the brain which is so affected. If the cerebrum alone is involved, coma appears; if the pons varolii and medulla oblongata alone, convulsions ensue; if both be

affected together the result will be combination of coma with convulsions. This suggestion attracted a great deal of attention, though its author modestly, did not claim for it any position higher than a mere hypothesis. Experiments were carried out in an endeavour to justify the suggestion, and in 1864 Munck published results of a series of experiments which he claimed as supporting Traube's hypothesis. He stated that by tying the ureters and the jugular veins in animals, and shortly afterwards injecting water, he produced uraemic attacks; and that he prevented this occurring when, by tying the carotid arteries he prevented the excess of blood pressure on the brain.[31].

As in the case of other suggestions, observations were immediately forthcoming to cast doubt upon the theory, but it slowly gained a surer footing, and Grainger Stewart, who in 1871 published the second edition of his book "Bright's Diseases," writes of it as follows: "The hypothesis is well worthy of being carefully investigated, for the condition of the brain met with in fatal cases of uraemia often accords with it, at least in the chronic cases in which death occurs from uraemia." He criticised it, however, as being unable to explain uraemia in acute cases.[32].

In the year 1867 Dr. Rommlaere of Brussels made

the important suggestion that the nervous symptoms were not to be ascribed to any one cause, but to many causes in combination. He combined several of the previous theories and stated, "when the functions of the kidney have been interrupted, not only does the waste azotised matter cease to be eliminated, but water accumulates in the system causing impoverishment of the blood, and increased tension of the blood vessels." To the combined action of all these he referred the nervous symptoms[33].

This is the first reference to the possibility of there being more than one factor concerned. Before this investigators had been seeking for one agent to account for all the symptoms.

During the preceding twenty years, although the "urea retention" theory had been overshadowed first by that of Frerichs and later by that of Traube, yet it was by no means forgotten, and a great deal of experimental work had been carried out in association with it. This culminated in 1868 when Voit published, in the Zeitschrift für Biologie, the results of a series of experiments which were to revive its popularity once more. The objections which had caused this view to be discarded were drawn partly from experiments on animals, partly from clinical observations of Bright's disease. Experiments had seemed

to show that urea, and even urine itself, could be introduced in large quantity into the blood of animals without giving rise to any ill-effects. Voit and Oertel maintained that although urea, when added to the food of a dog produces no symptoms so long as it can be fully excreted by the kidneys, yet if the animal is not allowed to drink any water, symptoms like those of uraemia appear.[34] In the same article Voit puts forward the complete "Retention Theory," viz. that uraemia is not due to the poisonous action of any one ingredient of the urine alone, and he attributed a considerable share in the production of uraemia to the "salts of potash."

The publication of Voit's experiments and conclusions not only revived interest in urea, but attracted the attention of investigators to the other ingredients of the urine. During the next few years the properties of each one of these were investigated and claimed to be more toxic than urea and therefore capable of producing the uraemic manifestations. Thus Jaccoud maintained that the retention of creatin was responsible for the symptoms,[35] and Landois carried out experiments to show that creatin and creatinin produced convulsions by direct action on the cerebral cortex.[36] Later, Gautier was to modify this theory by suggesting that

the creatin might become transformed into methyl-guanidine which is excessively poisonous.[37] At the same time experimenters were becoming less disposed to admit the accumulation of urea to be the active cause of the uraemic poisoning. Of all the normal ingredients of the urine the salts of potash had now come to be considered the most important. Astaschewsky of St. Petersburg,[38] and Feltz and Ritter of Paris,[39] each published results of experiments in support of this view.

Before this however, Rosenstein had doubted the possibility of any one theory being sufficient to explain the entire phenomena of uraemia, and stated that he believed that different symptoms might be due to different poisons. He cited the "variety of the uraemic symptoms as an objection to the unity of uraemia and of the uraemic morbid poison."[40].

During this period, although experimenters had succeeded in demonstrating that many of the normal ingredients of the urine were toxic, they were severely hampered in deciding the relative importance of each one by the lack of reliable chemical methods for the quantitative analysis of the blood. The natural result of all this work was to complete and consolidate the position of the "Retention Theory," viz., that the symptoms of uraemia are produced,

not by the retention of any one ingredient of the urine, but by the accumulation in the blood, and the combined action, of all the ingredients normally excreted in the urine.

Henceforward the history of the subject becomes "modern," and before proceeding to outline the further main points I propose to give a brief résumé of the arguments which led to the rejection of the main theories of the earlier period. During this period there were three outstanding theories; (i) That of Frerichs, (ii) The mechanical theory of Traube and (iii) The Urea Retention theory.

Frerichs' theory, first put forward in 1851, was the second of the important chemical theories. It had its genesis in the gradually growing dissatisfaction with the suggestion that retention of urea was the important factor. Believing therefore, that urea itself was not toxic and unable to produce the symptoms - for he had satisfied himself that neither the infusion of pure filtered urine, even when obtained from another species, nor the injection of urea or sodium urate, is attended by any pathological symptoms, even when such quantities of the latter are injected as could not accumulate in the blood during a retention of several days duration,[41] - Frerichs endeavoured to find a way in which it could

still play the leading part, and conceived the idea of its decomposition into ammonium carbonate which produced the symptoms. He endeavoured to support his theory by animal experiments and ingenious clinical tests. The suggestion, by its originality and plausibility attracted considerable attention and was widely accepted for many years. Much of the difficulty in proving or disproving this theory was due to the inadequate methods available for the chemical examination of the blood; for obviously, the justification of the theory must lie, not in proving that ammonium carbonate can cause convulsions when injected into animals, but in demonstrating its presence in the blood as a constant feature in uraemics. Chemists endeavoured to do this but without success. Oppler in 1861,[42] and Zaleski in 1865,[43] published observations casting doubt upon the suggestion. In 1868[44] Voit published results of exact quantitative experiments showing that the urea of the blood and tissues of the <u>living</u> organism is not transformed into ammonium carbonate, and that even when its conversion has begun in putrefying blood, its progress is very slow, much slower in particular than the putrefaction. Only in one region of the body does the conversion of urea take place rapidly, namely in the intestine. It was this fact that led

first Treitz,[45] and then von Jaksch[46] to modify the original theory. But here the ammonium carbonate always produces local effects, and never gives rise to general uraemic phenomena.[47] It is true that when injected in sufficient doses directly into the blood, ammonium carbonate may bring about convulsions and coma; nevertheless it was ultimately proved that all the early statements as to the ammonia content of the blood of animals deprived of their kidneys, or of uraemic persons were erroneous. Later analyses conducted by improved methods showed that although sometimes, but by no means invariably, the ammonia of the blood of renal cases exceeds the normal,[48] yet the accumulation is never sufficient to produce toxic effects.[49] Ammonia can only be detected with any degree of constancy in the vomited matter and diarrhoeic stools. There appears to be no doubt whatever that, if present in the blood at all, it is not in sufficient quantity to account for the effects attributed to it, and in fact there is not a particle of evidence to show that there is any regular increase of the ammonia of the blood in these circumstances. It is evident, therefore, that the modifications of Treitz and von Jaksch are also untenable.

In addition, Schottin[50] showed that the demonstration of ammonia in the expired air by

holding a glass rod dipped in hydrochloric acid before the mouths of uraemics - one of the clinical tests which Frerichs adduced in support of his view - failed completely in many uraemic patients; whereas it often succeeded in other patients who lay in a typhoid state from whatever cause, the carbonate of ammonia being set free from the dried secretions within the mouth, and not exhaled from the lungs.

For these reasons Frerichs' theory fell into disfavour, and twenty years after it was first put forward it had become of purely historical interest. The investigations of recent workers have entirely supported the verdict of the earlier investigators, and the hypothesis is not seriously considered at the present day.

Traube's theory, put forward about ten years after Frerichs', at a time when the latter, although still the subject of dispute, was commencing to fall into disfavour, is one of the most important of the older theories.[51] It was not entirely new, as Osborne in 1837 had endeavoured to explain the symptoms as being due to inflammatory alterations of the meninges of the brain, or hyperaemia of the cerebral vessels. Traube substituted for these vague and partly erroneous views, a well considered mechanical theory recognising the determining element to consist in the combination of hydraemia and rise of arterial

pressure, so common in cases of nephritis. When, owing to any accident, a sudden rise of this high tension, or increase of the 'hypalbuminosis' occurs, there is oedema of the brain with anaemia of its substance producing coma or convulsions, according to whether the cerebrum or mid-brain be involved.

The only early attempts to substantiate the theory experimentally were those of Munck, published in 1864.[52] Munck's experiments cannot be accepted as reliable, however, as, with the jugular veins and ureters ligated, it is not surprising that the brain should become oedematous, rather would one be surprised if it did not.

Cohnheim[53] conducted experiments in an endeavour to produce a state of persistent general high arterial tension with hydraemia. He infused enormous quantities of a 0.5 per cent. salt solution into a vein of a healthy dog, producing an arterial tension which persisted for hours at the highest normal values ever observed, and found that the brain and its membranes remained no less dry than in a normal healthy animal. His experiments also showed that it is incorrect to assume that hydraemic blood transudes more readily than does blood of normal composition, a statement which holds equally whether the arterial pressure be high or low.

Experiments of this nature are of little value, however, unless oedema of the brain be a constant finding in uraemia. It was soon found that this was not the case. Whilst it is true that the brain of persons who had died during an attack of uraemia were sometimes found to be moister than usual, yet in many instances the brain after death was found to be perfectly dry. For this reason Bartels[54] suggested that when the brain is oedematous, this is much more likely to be an effect than a cause of any convulsive seizures. An opinion which was supported later by Cohnheim[55] and others.

Every part of Traube's original theory, therefore, has been shown to be untenable. Although this is the case, - for at that time workers were endeavouring to find one explanation for all the symptoms - yet oedema of the brain can cause convulsions, and it is still maintained by certain investigators that some of the symptoms of uraemia are due to a localised cerebral oedema, but as yet, the weight of evidence is against this view.

The third great product of this period in the history of the subject, was the hypothesis that urea, being imperfectly eliminated by the kidneys, accumulated in the blood, and by its toxic action caused the symptoms. The suggestion is important,

and merits special consideration, if only because it gave the name to the condition.

The theory seems never to have been generally accepted, yet workers were very loath to reject it entirely, and always fell back upon it when other suggestions became untenable.

The theory first became widely considered about 1840,[56] and was the natural outcome of a process of elimination of the facts of the disease as then known. Suggestions attributing the symptoms to albuminuria, dropsy, hydraemia and cerebral oedema had all been tried and discarded. The presence of urea in the blood, and also in the vomited matter, and in effusions, had been demonstrated, and it was natural that the attention of investigators should become turned towards it. From the first it was disputed however, and, as has already been described, Christison's description of a case of anuria without convulsions or coma cast doubt upon its validity. Animal experiments were performed with varying results, and the later ones tended to show that urea, and even urine itself, could be introduced into the blood of animals without giving rise to any ill effects. Similarly, clinical findings were at variance with the theory, and the presence of symptoms was found to bear no constant relationship to the presence of urea in the blood, which might be loaded

with urea without any such symptoms appearing.

The position in 1851 was,therefore, that whilst the majority of investigators considered the evidence unfavourable to the acceptance of the theory, yet nearly all believed it to have something to do with the production of the symptoms, mainly due to the lack of a more acceptable hypothesis. Then came Frerichs' theory, and later that of Traube, both of which were eagerly adopted, and the urea theory for the time being became overshadowed. When these theories were rejected in their turn, the urea theory was resuscitated, partly because there was no more satisfactory suggestion - thus, Pye-Smith[57] in his "Principles and Practice of Medicine," (Fagge), writes, "Recent observers have recently fallen back upon the older and simpler theory, which supposes that the symptoms of uraemia are due to the presence in the blood of urea," - and partly on account of the researches of Voit and Oertel,[58] which had again given prominence to urea and suggested that it had toxic properties. Other workers performed similar experiments with very variable results. While most succeeded in producing symptoms similar to those of uraemia when urine was used in the experiments, very few claimed to have succeeded when using urea. Thus, Astaschewski,[59] in 1881, observed that a dog with ligatured ureters, into which he

introduced by the femoral vein the whole of the urine passed by it in three days, in concentrated form, became restless, was attacked by vomiting with acceleration of the pulse, soon developed terrible convulsions, and died comatose 100 minutes after the injection; but he failed to produce any uraemic symptoms by injecting urea, even in enormous quantities.

One of the main reasons why urea was believed to be the toxic factor was the lack of a precise knowledge of the chemistry of the blood; one of the very first series of clinical blood analyses - that by Garrod[60] - not being performed until 1848, one year after uraemia had received its name. Urea was the only one of the normal urinary ingredients that could be satisfactorily demonstrated as retained in the blood. By the time of its second incarnation however, it was realised that other substances deficient in the urine were retained, and this naturally detracted from the value of those earlier experiments in which filtered urine was used. Voit himself appreciated this fact, and demonstrated that the salts of potash are more toxic than urea. Other workers experimenting with other substances such as creatinin, were able to demonstrate the toxicity of these. Roger[61] states that there are at least eleven toxic substances in normal urine, and each one to a greater degree than urea. This destroyed

any grounds that remained for believing urea to be the sole factor in the causation of uraemic symptoms and led naturally to the development of the theory that the symptoms are due to accumulation in the blood of all the ingredients normally excreted in the urine. More recent work has fully justified the opinion that urea is practically non-toxic. Some years ago large amounts of urea were given for tuberculosis.[62] There is no evidence that it was of benefit, but it certainly was quite harmless.

There is then, not the slightest evidence that urea alone is capable of causing uraemia, though at least one modern writer is not prepared to disregard it as a contributory factor (Wells),[63] and these same arguments are equally applicable to each of the other normal constituents of the urine individually.

Sufficient has been said about each of these three theories to indicate the arguments which led to their rejection. It is not necessary to consider further either the numerous individual suggestions, or the isolated remarks bearing upon one or other of these theories, which are to be found in many communications, (e.g., Feltz and Ritter, "De l'urémie expérimentale," Paris, 1881; von Noorden, Metabolism and Practical Medicine." Vol: II. 1907. p.501).

since in the main their findings are in keeping with the considerations already expressed above.

The "modern" period commences with the predominance of the Retention Theory. It did not attain this position without difficulty however; the two main obstacles being that sometimes cases occurred with very marked diminution of urine but without uraemic symptoms supervening, whilst in others convulsions occurred with an aboundant elimination of urea. These were the reasons which prevented it from becoming accepted when it was first put forward in 1868 by Voit, who, recognising the absence of other substances from the urine, believed that uraemic symptoms might be produced by "any substance which is not a normal constituent of the body if it accumulates in large quantities, and is not eliminated."[64]

This vague statement was later opposed by Roberts,[65] to whom we are indebted for a clear recognition of the clinical fact that symptoms altogether unlike uraemia, and following a different course, are shown by cases in which the failure to eliminate urea and other ingredients of the urine is absolute, but in which the cause of the suppression is not due to affection of the kidneys, but to obstruction of the ureters. He believed that the absence of uraemia in these cases showed that where there is healthy

kidney substance with an active circulation through it, the waste products which should be excreted in the urine undergo some chemical changes that render them incapable of producing uraemia, notwithstanding that they are retained in the body.

Roberts maintained that the cause of uraemia is the accumulation in the blood of products intermediate between urea (or uric acid) and the albuminous substances from which it has its origin, such as creatin and creatinin, hypozanthin and zanthin, or leucin (amido-caproic acid), or aspartic (amido-succinic) acid and tyrosin.[66] As has already been indicated, the suggestion that any one of these individually is responsible for the symptoms, cannot be maintained, but the principle underlying this opinion of Roberts' has developed into the modern theory that the cause lies in some derangement of metabolism.

On account of those clinical facts which are against the retention theory considerable ingenuity was expended in endeavouring to retain the hypothesis while explaining the variations.

In 1881, Fleischer[67] published results of a series of experiments dealing with the relation of uraemic symptoms to the excretory action of the kidneys. He made careful analyses of the urine passed by persons

affected with Bright's disease, and compared them with analyses of the urine of healthy persons under the same conditions. He found as a rule that the amount of urea excreted by those who had Bright's disease was much diminished; but that when uraemia occurred, the amount of urea was increased far beyond the normal, either on the day of the seizure, or a day or two later. He concluded that, when the accumulation of urea and other urinary constituents reaches a point at which the system ceases to be indifferent to their presence so that uraemia results, they at the same time stimulate the heart and kidneys to expel them.

This observation achieved some prominence as tending to explain those cases of uraemia in which examinations had shown either aboundant urea in the urine, or no marked excess in the blood, the suggestion being that those previous observations might not have been made at the proper period of the disease.[68]

Other attempts to explain the inconstant relationship between the retention of urea and uraemic attacks were (i) the assumption of certain physical states, and (ii) predisposition on the part of the patient; thus, Fagge in 1885 writes,[69] "After all, however, such facts are entirely in accordance with clinical experience in general. The effective opera-

tion of all causes of disease is liable to be interfered with by unknown conditions, of which the resistance of the patient's tissues is the most important. It is a remarkable fact that uraemia is seldom met with in persons advanced in years; perhaps this suggests that a predisposition on the part of young subjects is a factor in its etiology."

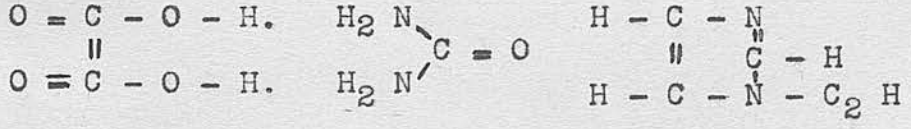
In spite of these attempts to explain the cases in which the behaviour of urea was not in accordance with the general rule, the Retention Theory had not yet become generally accepted, and the same authority in summing up the general opinion held at that time wrote, "There seems to be no doubt that uraemia is produced by the poisonous action upon the nervous centres of materials accumulated in the blood as the result of defective excretion by the kidneys. But it is still uncertain whether this action is excited by one substance or by more."[70] Similarly Cohnheim, in his "Lectures on General Pathology" 1882, after a very full and careful discussion of the various suggestions, supports the retention theory as the most probable, though he states that possibly different substances may produce the pernicious effects on different occasions.

Most of the investigations, and all the important chemical theories had so far centred round the

normal ingredients of the urine or their immediate precursors. The suggestion was now made that the symptoms might be due to the accumulation of alkaloids in the blood. Gautier[71] made the suggestion that methyl-guanidine, which is excessively toxic, might be formed from creatin and account for the symptoms. Brieger's[72] investigations led to a similar suggestion, that one set of poisons is probably allied to uric acid, and may include guanidine, methyl-guanidine and other derivatives of urea.

In 1899 Lauder Brunton[73] made a new chemical suggestion. He thought that a substance chlor-oxal-ethylene might be the toxic agent and suggested that it should be sought for in the blood. He did not, however, claim to have found it himself. The grounds upon which he based his hypothesis were:- (a) That he had often been struck by the extremely rapid pulse in cases of uraemia, although there was no rise of temperature to account for it. The rapidity could only occur if the vagus were paralysed or inactive, and resembled so much the action of atropine that it suggested to him that one should search for an atropine-like body as the cause of the symptoms. (b) He had observed that in various disorders of nutrition in which uric acid was increased, oxalate of lime was also frequently increased, and that

therefore one might naturally regard compounds of oxalic acid as among the substances likely to give rise to the symptoms if retained in the body. (c) There is a substance allied in its chemical constitution to oxalic acid - oxalethylene - which has the power of paralysing the vagus and producing great rapidity of the pulse just like atropine, the action of which it also resembles in causing dilatation of the pupil and exciting the brain. (d) When one atom of hydrogen in this body is replaced by chlorine so as to form chlor-oxal-ethylene, one obtains a body which no longer dilates the pupil, acts upon the brain like morphine, but still paralyses the vagus; thus producing a group of symptoms closely corresponding to those occurring in certain cases of uraemia. He gave the following formulae:-



Oxalic acid Urea Oxalethylene.

I can find no reference indicating that this suggestion was ever seriously considered, and none referring to any experiment designed to find the substance, if present in the blood.

Meanwhile, Bouchard[74] had been conducting a great many important researches into the subject of auto-intoxication. He insisted strongly on the fact that normal urine is toxic, and that its toxicity depends upon a number of substances, more especially salts,

pigments and certain unknown constituents, and that the nitrogenous extractives, and more especially urea, possess but little poisonous action. He conducted a series of experiments to show that a certain quantity of urine injected into the circulation is fatal; in some cases death was preceded by convulsions, in others by coma; in nearly all contraction of the pupil and failure of the respiration were marked symptoms. By comparing the amount of urine injected with the weight of the animal, he established what he called a "urotoxic coefficient." He stated that in many cases of uraemia the urine loses a proportion of its toxicity, and he deduced from this that the toxic principles are retained and produce the symptoms.

Bouchard's work was a most thorough investigation, and was widely accepted, and the estimation of the urotoxic-coefficient was, in France, considered an essential part of the investigation of nephritis for many years.

The publication of Bouchard's conclusions in 1887 in his work on "Autointoxication" was the final factor in the consolidation of the position of the retention theory. This hypothesis, though still believed by many to be incapable of accounting for all the symptoms, became tacitly accepted by physicians generally. This opinion was reflected in the text books of the time which gave it as the definition

of uraemia. In Osler's "Principles and Practice of Medicine" 1895, only two theories are considered; (i) the "Retention" theory, and (ii) Traube's theory, the latter being adversely criticised.[75]

The problem of reconciling the theory with the difference between the symptoms of "uraemia" and "latent uraemia," still remained, however.

All the theories so far put forward had been either chemical or mechanical. A new and original suggestion was now presented in an entirely different field. In 1892 Brown-Séquard, who with Claude Bernard was the principal founder of the doctrine of the internal secretions through his production of experimental Addison's disease in 1852, promulgated the theory that the kidney forms an internal secretion.[76] In 1897 Ajello and Paraveandalo[77] published the results of a series of experiments in justification of this view. They claimed that these experiments indicated that the renal secretion is necessary to health, and that uraemia follows on its deficiency or suppression.

In 1898 J. Rose Bradford[78] described some experiments of his own upon dogs in which he removed part of one kidney and then extirpated the other. As the animals before death passed a greatly increased quantity of urine and more than the normal amount of

urea, he claimed that the kidney furnished an internal secretion which regulated nitrogenous katabolism, and that in its absence this went on unchecked. The symptoms observed were, however, entirely different from the classical symptoms of uraemia. In no case were coma, vomiting or convulsions observed.

Although Rose Bradford's conclusions were doubted later, especially after the criticisms of Bainbridge and Beddard,[79] yet it is generally accepted that renal juice does contain a substance "renin," which has pressor properties similar to those of adrenalin.

Allied to the theory of the loss of the internal secretion of the kidney was the suggestion that the symptoms might be due to nephrolysins set free from the damaged kidneys. Many investigators devised numerous experiments in an endeavour to prove that autolytic products exist in the blood under such circumstances, but the results were so variable that the theory was never enthusiastically received, and it was never considered as more than a possibility.[80]

Such then was the position at the beginning of the present century. The theory of the loss of an internal secretion of the kidneys was still under discussion, and the majority of observers considered

uraemia as dependent upon the presence of toxic material in the blood, and the excitation of the nervous system by the poison. No poison capable of producing all the symptoms had been separated and identified, and it was believed that more than one toxic body was present. The generally accepted origin of the poison was, "that substances which ought to be, and normally are, excreted are retained."[81].

For a few years no important additions were made to the knowledge of the subject, but there was a growing body of opinion in support of a view expressed long ago by Perls and Schottin[82] that although the exciting cause of the uraemic symptoms is the accumulation of toxic bodies in the blood, yet the origin of these substances is not the retention of a product normally excreted, nor the decomposition of any such substance, but that they are due directly to the formation of products of disordered metabolism.

Ascoli[83] who had been making a very thorough and critical inquiry into the total toxic effects of all the known urinary substances, believed them incapable of explaining all the uraemic symptoms.

Carl von Noorden of Frankfurt,[84] in 1907, published his account of a very comprehensive inquiry into the subject of disorders of metabolism. His conclusions disproved all the older theories regarding ammonia, creatin, uric acid, potassium salts etc.,

and supported the opinion of Ascoli. But he did not believe that one could entirely exclude the possibility that poisoning may be directly caused by urinary substances, as he considered the available methods for estimating the degree of toxicity very "rough and inadequate." He made a further suggestion, that whereas the substances have always been sought for in the blood, they have special affinities for certain cells in the body, just as morphine, or the toxin of tetanus combine preferentially with cells of the nervous system. The question of the localisation of these extractives in the various tissues requires investigation therefore before it can be definitely decided that they are not the cause of uraemia.[85].

From this time onwards, the theory that the poisoning is due to the retained ingredients of the urine gradually became less and less popular. Investigations became concerned with the theory that the poisons are the products of abnormal metabolism.

During the past twenty years, investigations have centred round this hypothesis, and, whilst no new theories regarding uraemia as a whole have been presented, yet there have been important changes in the conception of the condition, which have developed as the natural consequences of research in this direction. Thus, whereas formerly investigators

sought for some explanation of uraemia as a whole, the modern tendency is to try to explain the individual symptoms. The whole trend has been towards simplification, which has been made possible largely on account of the improved classifications of Renal Diseases, and it is probable that soon "uraemia" will cease to be described as a separate entity, that the name will be dropped, and that the symptoms will be described under the conditions with which they occur.

Another change has recently taken place in the general outlook upon the origin of the symptoms. Whereas formerly their origin was assumed to be entirely renal, the opinion is now spreading that this was a quite illogical assumption, for the functioning of other organs is so closely linked with the excretory functions that it is reasonable to suppose that interference with the latter would reflect back upon the former, and that the symptoms might be due to their derangement. Similarly it is reasonable to suppose that the cause which is able to produce the progressive lesion of the kidney is equally capable of affecting other organs, and that some of the symptoms may be due to such affection. This theory of the pathogenetic significance of extra-renal factors was emphasised comparatively recently by Vaquez and Volhard.[86].

This change in the conception of the site of origin of the toxins is indicated by H. Batty Shaw who writes, "I can state from a careful inquiry into the views held by responsible authorities whose statements were published in the following years, 1896, 1904, three in 1915, and one in 1920, that the cause is resident in the kidneys; so uraemia in the past has been referred to fault in the kidneys till within the last few years."[87].

One reason why the kidneys were regarded as the source of the uraemic poisons was, that experiments carried out in 1865 by Zaleski[88] had established the fact, later confirmed by Perls and Schottin,[89] that urea is formed by the kidneys from nitrogenous material in the blood. Recent work, however, makes it seem probably that the liver is the chief site of urea formation, but it is also probable that it can be formed in other organs.[90]

For this reason the liver is now regarded as an important probable source of some of the toxic products.

The evolution of this opinion has been made possible by the rapid advances in the technique of biochemistry. Although, as has been mentioned, blood analyses were made many years ago, yet the methods available were quite inadequate. Although Christison, Babington and Barlow searched for, and

found, urea in the blood of uraemic subjects, the first important series of blood analyses were carried out in 1848 by Garrod.[91] In 1850 Carl Schmidt described researches on the ultimate analysis of blood from fatal cases of cholera,[92] but very little work of outstanding value was done until 1913, in which year Bang introduced his micro-chemical analyses, and Folin began to publish his methods,[93] out of which grew his present well known system. Van Slyke also published analytical methods in the following year.[94]

Most modern researches, therefore, depend upon the belief that the symptoms called "uraemic" are due to an intoxication: that they cannot all be ascribed to the effects of one toxin: that some – those occurring in conditions of "anephrexia" (latent uraemia) are due to the retention of products which should normally be excreted in the urine, (Leiter)[95]: that the other more dramatic symptoms are due to the circulation in the blood of abnormal products of metabolism, possibly on account of derangement of the functioning of the liver: whilst the remainder are due to alteration of the state of the blood, or to the efforts of the body to eliminate the toxin by channels other than the kidneys.

By means of the Folin and Wu system it is

possible to obtain a fairly accurate idea of the distribution of nitrogen throughout the blood filtrate. The non-protein nitrogen can be divided up between the urea, uric acid, amino-acids, creatinin and similar bodies. If all the well-known nitrogenous bodies be estimated, and their nitrogen content worked out, it would be expected that the sum of these figures would approximate to the non-protein nitrogen value. This, however is not so, and there is a relatively large part of the non-protein nitrogen of unknown constitution. If renal function be impaired, nitrogenous bodies accumulate in the blood, and this unknown fraction is also increased.[96]

It is in this unknown fraction that the toxins which cause uraemia are believed to exist.

Several toxic substances have been isolated, amongst the earliest was choline,[97] a substitution product of ammonia formed from breaking down of the complicated fat of the nervous system. More recently Golla[98] has suggested trimethylamine, which experimentally produces epileptiform convulsions, and is increased in the blood of uraemic patients, but not in cases of obstructive suppression.

Much of the recent chemistry is still awaiting development. Hartman[99] in 1915 suggested that the

substance which causes the characteristic odour of the urine may be responsible for some of the symptoms. He isolated and described this substance under the name of "urinod," which he believes to be a cyclic ketone with the empirical formula C_6H_8O; it is highly toxic and causes mental symptoms. This observation awaits confirmation.

In 1915,[100] and again in 1921,[101] Foster described the finding of a toxic base in the blood of uraemics, capable of causing convulsions. Further development of this work is also lacking.

Further results of recent biochemical research are given in a later section.

Having indicated the lines along which modern investigations are being conducted, this study of the Etiology of Uraemia, from the strictly historical aspect, is concluded.

PART II

The Symptomatology of "Uraemia."

There is a great diversity of opinion as to what symptoms may rightly be included in the "uraemic" syndrome. In France, for example, authorities have given the name "petite urémie"[1] to all the symptoms which usually accompany renal disease, such as increased blood pressure, cardiac hypertrophy, headache, digestive troubles etc., instead of reserving the word for a condition characterised by unconsciousness and convulsions, as is more customary in this country. These divergent views may be attributed to the fact that, the limited significance of the original term having passed, "uraemia" has been retained as a convenient expression under which to group any unusual toxaemic symptoms which may arise in the several forms of renal disease, or with any interference with the ordinary eliminative function of the kidneys, possibly as a result of disease of some other organ. As a result, the symptoms described as "uraemic" are now so numerous that there is considerable difficulty in attempting to make a suitable classification.

The original manifestations, which later became separated as "uraemia," were, "symptoms which also very commonly present themselves in the course of the same disease (Bright's Disease), but are not essential to

it . . . . various manifestations of derangement in the cerebral functions; headache, drowsiness, delirium, epileptic seizures, apoplexy."[2] These symptoms were known as the "head symptoms of renal dropsy" and it was recognised at an early period that they might be the chief symptoms of Bright's disease. In 1839 Addison[3] described a case which exhibited "a sudden attack of coma with stertor, or, in other words, apoplexy." Though Fagge[4] remarks that post-mortem experience did not support Addison's view that cerebral haemorrhage might be simulated by uraemia, it was to Addison's endeavour to distinguish between these two conditions that we owe his observation of the often typical hissing stertor in "uraemia," "as if produced by the air striking against the hard palate, or even the lips, rather than against the velum and the throat as in ordinary apoplectic stertor."[5]

In 1840 Bright[6] recorded a case in which for two days before death there occurred a very distressing and almost incessant twitching of the muscles, which increased until the arms and the legs were forcibly drawn up and the face was distorted by spasms, yet the faculties of the mind were perfect to the last.

It was not long before these "head symptoms" came to be associated with the retention of urea in the blood and grouped under the term "uraemia."

As the subject of Renal Diseases was more closely studied many additional symptoms were described, and when doubt was cast upon the toxicity of urea, the term "Uraemia" came to include any symptoms which may occur when there is a "retention in the blood of the excrementitious substances normally excreted by the kidneys."[7] This considerably widened the scope of the term, and it was classified as <u>acute</u> or <u>chronic</u>, according to its mode of onset; or <u>latent</u>, when the most characteristic symptoms were absent, although according to the accepted ideas conditions were most favourable for their occurrence. The symptoms, however, were still considered to be complications of primarily renal conditions. It is now realised that nephritis, using the word in its strict sense, is not a necessary precursor of "uraemia." Batty Shaw records a case.[8]

> "A woman cook, aet. 52, developed cough, "shortness of breath, frequent vomiting and pal- "pitation; then both legs became dropsical and "she took to her bed. The expectoration was "never purulent, but was white and frothy. "She was found to have double mitral disease; "albumin was found in the urine, a trace to "a thick cloud. After a little more than a "month her condition improved greatly, and "she was able to be up and about in the wards, "but in about five weeks dropsy recurred and "became so severe that Southey's Tubes had to "be used. Then she became very short of "breath and cyanosed, and had a fit which was "described as uraemic; during the next few "days these uraemic fits were repeated. At "the post-mortem examination of the kidneys "only 4 per cent. of the Malpighian corpuscles "were found to be destroyed, and only in some "of the tubes was the epithelium atrophied;

"the kidneys were congested, and were passed
"as examples of a cyanotic or cardiac kidney
"dependent upon the double mitral disease
"which was found."

A consideration of this case makes it quite clear that "uraemia" is not a feature peculiar to the recognised primary diseases of the kidneys, for it may occur when the kidneys are secondarily changed in the final stages of heart disease. Similarly, cases have been described in which both the kidneys were out of action, yet "uraemia" proper in any of its phases did not occur.

It would appear, therefore, that whilst "uraemia" occurs most commonly in almost all diseases of the kidneys - in acute and passive congestion, in all forms of nephritis, in amyloid disease, in tuberculous, calculous and cystic diseases, in hydronephrosis, and in consecutive nephritis - yet it may occur in any condition in which the functioning of the kidneys is interfered with, either secondarily, e.g., in cholera or cardiac disease, or even where the kidney shows few signs of any disease, e.g., the complete suppression which may follow severe injuries to various parts of the body, or operative procedures on any part of the urinary tract.

Another outstanding feature is the wide difference between the symptoms produced when the kidney is partially damaged by disease (uraemia), and those which occur as the result of total suppression of the

urine, the kidneys showing no marked indications of disease (latent uraemia). The former I have termed "Dysnephrexia," and the latter "Anephrexia." "Dysnephrexia" should not be separately described as an entity; it is a complication, and may occur in many morbid conditions, whilst there is reason to believe that many of its symptoms are not directly referable to the kidneys. The symptoms of "Anephrexia" on the other hand are very definite and constant, and I would suggest that this term might replace "latent uraemia" or any of its synonyms.

Under these two main headings I propose to retain the old classification in which the symptoms are described according to the systems affected. Whilst this method is open to the objection that many of the symptoms described under other systems may really be referable to a cerebral cause, yet for the purpose of this Thesis it is the most convenient.

SYMPTOMS ASSOCIATED WITH "DYSNEPHREXIA."

Grave symptoms occur most commonly in the course of chronic renal disease, or else during the course of acute nephritis, when they may be very violent and severe, as in scarlatinal nephritis. Some of the most remarkable may, however, occur suddenly, either in the midst of apparently robust health, or when the symptoms of some chronic renal disease have existed

for some time, but, owing to their apparently trivial nature, have either been overlooked or neglected, as in granular or cirrhotic kidney.

The more important symptoms may be conveniently classified clinically as (i) Cerebral, (ii) Respiratory, (iii) Gastro-intestinal. These are not all clearly differentiated from each other, however, and all may occur together.

(i) CEREBRAL SYMPTOMS:-

The more acute nervous symptoms occur chiefly with acute nephritis, especially when resulting from scarlet fever; they may arise in chronic nephritis when the urine is reduced in amount in consequence of a subacute exacerbation; they often accompany non-obstructive suppression of urine due to catheterism, abdominal injuries or diseases, or operations upon the kidneys and bladder. Severe renal congestion, the result of disease or of poisons or toxins developed in the course of disease, is also frequently followed by acute symptoms.

The onset of such symptoms may be without any warning, or it may be preceded by various premonitory symptoms.

Premonitory Symptoms:- The most marked premonitory symptoms are constant headache, mental apathy, drowsiness and vertigo; nausea or even vomiting, may sometimes occur; while in a few cases

there may be severe dyspnoea. Occasionally there is a marked diminution in the quantity of urine. Attention has been directed to a strange, fixed expression of the face, to a dragging pain in the extremities, or to a transient rigidity of the lower jaw, or of one of the limbs.[4] Tremors similar to those of paralysis agitans have also been described; frequently there is twitching of the face and hands. Abnormal hardness and high tension of the pulse commonly precede the more obvious symptoms. The twitchings may be gradually aggravated into epileptiform attacks, or the drowsiness deepen into coma.

Convulsive Attacks:- The symptoms fall into two categories: (i) Those due to paralytic affection of the brain and of some of the sensory centres, and (ii) those referable to irritation of the motor tract, leading to tonic and clonic convulsions. This latter type in its pure form is not common, except in eclampsia; but epileptiform seizures of a similar character occur in association with other groups of symptoms. Sudden seizures of very great violence may occur in cases of granular kidney associated with high blood pressure. These epileptiform attacks are most prone to occur when the arterial blood pressure is very high, and in some instances extremely high arterial pressure may be present without extensive

degeneration of the arteries. (The important relationship between hypertension and "uraemia" is fully discussed in later sections).

The immediate onset is often a sudden paroxysm of convulsions of an epileptiform type which may or may not have been preceded by some of the premonitory symptoms. The patient becomes unconscious and convulsed, the fit beginning, like other forms of epileptic seizures, with movements involving the small muscles, then spreading rapidly to the whole body; sensibility and reflex action are lessened and frequently abolished, and the knee-jerks are exaggerated. In slight cases the spasms may be confined to passing contractions of the muscles of the face, or of the extremities, but in severe cases they may be more violent and general, and the whole body may be shaken with violent convulsions, while the respiration falters and becomes stertorous. In such severe cases the patients foam at the mouth and grind their teeth, while faeces and urine may be passed involuntarily.

The clonic spasms usually only last a few minutes. Should but one fit occur, the convulsions cease gradually, and the patient passes into a drowsy or comatose condition, from which he may be partially roused for a short time, and again appears to fall asleep. After an interval, ranging from a quarter of an hour to several hours, he awakes

as from profound sleep. Generally, after a few hours or days, the attacks return with renewed vigour, the intervening stupor becomes more profound, and at last passes into permanent coma. Death may occur during the comatose state, or at the height of the convulsive seizure.

The clonic convulsions are sometimes unilateral, and may be preceded or replaced by tonic spasms, constituting "tetanic uraemia," which may be of long duration.

During the convulsive attacks the temperature is usually low, or even subnormal, but in exceptional cases, especially if the fits are very frequent and severe, the body temperature may rise considerably, and there may even by hyperpyrexia without the presence of any gross inflammatory lesions of the lungs, or elsewhere, to account for the height of the fever. Low temperatures ranging from 86.1° F. to 94.4° F. have been noted in uraemia consecutive to diseases of the urinary passages;[9] it has been suggested that low temperatures are more frequent when the patients are advanced in years, or when the attacks occur in conjunction with exhausting conditions, such as vomiting, diarrhoea or haemorrhages, or in connection with cancerous cachexia. In the rare cases in which the temperature has been found to rise as high as 105.8° F. or even 107.4° F., this

sudden elevation has always been followed by a rapid fall.

During the convulsions the pulse is usually accelerated. Wagner[10] states that the pulse may be so slow as 60 or even 40 beats in the minute as a prodromal symptom. After the spasms it returns to its natural rate, or may become slower. Wagner records a case in which the pulse remained between 44 and 64 for the next fortnight following convulsions.[11].

The pupils usually retain their sensitiveness to light, though authorities are not agreed about their size. Fagge[12] states that they are more often contracted or normal, which is in accordance with my own experience, but Wagner[13] states that they are as a rule dilated, seldom small. Others maintain that no definite change occurs with sufficient frequency to justify a general statement.

In many cases, before the insensibility following one series of convulsions has passed off, another sets in; in this way twenty or thirty paroxysms may occur in succession, simulating the "status epilepticus." This is very likely to prove fatal, though even after a series of fits it is not uncommon for recovery to take place. A single paroxysm seldom ends fatally, but Fagge records a case of a woman aged 30 who died after one seizure in Guy's Hospital

in 1862.[14]

The convulsions may be followed by dimness of vision, or even by blindness, which may be transient or permanent; or ocular phenomena may be the first symptoms. The condition has been attributed to transient oedema of the retina, or to oedema of the brain. Ophthalmoscopic examination during amaurosis generally gives negative results, and the pupillary reflex is intact. Vision may be regained after twenty-four or thirty-six hours, and recovery has been known to occur even after 17 days of total blindness.[15]

Acute Mania and Delusional Insanity ("folie brightique").

Attacks of acute mania, or of delusional insanity are not common manifestations, but are seen occasionally in cases of contracted kidney in young adults; sometimes in cases in which symptoms of disease have existed and been recognised for some time, in other and more obscure cases in which the onset of violent mental symptoms has been the first, and very misleading indication of the underlying malady. The patient is excited, restless, noisy and sometimes very violent; in two cases recorded by Rose Bradford[16] cataleptic phenomena were present at intervals. The excitement soon gives way to drowsiness, and then to coma and other of the more typical symptoms. In cases of delusional insanity, granular kidney, otherwise un-

suspected, is often found in asylum post-mortems.

Hemiplegia, Monoplegia:- An attack of convulsions is sometimes accompanied or followed by some form of motor paralysis, especially hemiplegia. A hemiplegia, or even a monoplegia may occur suddenly, without any gross lesion being found after death. Such paralyses are frequently transient and incomplete, but the reflexes are abolished or diminished, and the condition may be followed by contracture. When the face is affected ptosis is exceptional, but conjugate deviation of the eyes has been observed.[17]

Insomnia:- A most persistent inability to sleep may be the most marked symptom, associated with twitching, cramp and hiccough; but the mind remains clear and there is no coma; death occurs, often suddenly, from respiratory failure.

Coma:- Coma may occur as a terminal phase after the occurrence of any of the acuter symptoms, but more frequently without any convulsions the patient passes into a state of drowsiness which deepens into coma. The onset is usually gradual, and its origin may be unrecognised, or attributed to some other cause. Frequently there is complaint of dull headache affecting the occipital region, or less commonly the frontal, and when paroxysmal it simulates violent migraine. It may be accompanied or replaced by giddiness and drowsiness, or by lan-

guor and inertia, which gravely interfere with all mental and muscular efforts. Sometimes the coma is preceded by cramps, especially in the calves, and twitchings especially of the forearms, and the latter are usually to be observed during the progress of the case. The symptoms are peculiarly persistent, though there may be brief intermissions. They may be succeeded by respiratory and digestive symptoms, especially nausea and vomiting, sometimes by partial or complete loss of vision, and there is always a considerable fall in the body temperature. The lethargy increases with perhaps attacks of delirium or convulsive seizures, till stupor and coma supervene. When coma supervenes without convulsions the tongue becomes dry and brown, sordes collect upon the teeth, and the condition resembles that of an advanced stage of typhoid fever.

In a case of this type recently recorded by Tirard,[18] aphasia and marked contraction of the pupils were the chief signs preceding coma.

Mental derangements may occur with this type of case, and include hallucinations, terror, delusions of persecution and excessive motor irritability. The type of delirium is generally quiet, but occasionally it may be furious. Binswanger,[19] who describes several cases, has found that exacerbations and remissions of the renal disease keep pace with similar variations of symptoms of mental derangement.

Other symptoms which may occur and must be considered nervous in origin are, singing in the ears, difficulty in hearing, or complete deafness, which may suddenly supervene and depart as quickly. Uraemic deafness has been attributed to minute haemorrhages in the cochlea, but, from the rapidity of recovery, it is far more probable that it generally depends upon some toxic influence acting upon the auditory centre. Severe itching of the skin is a very frequent and very distressing symptom. In old people it leads to intense pruritus which defies local treatment. The irritation may disturb sleep, all forms of acroparaesthesia may occur, especially at night, and even when sufficiently comatose to resist all efforts to rouse them, the patients may continue to rub and scratch themselves. Cutaneous hyperaesthesia with burning or stabbing sensations is sometimes met with.

Generally the cerebral type is rapidly fatal. Convulsions and amaurosis, though more striking, are less grave than the other symptoms. Langdon Brown[20] records seven instances of convulsive seizures during the epidemic of acute nephritis among the Expeditionary Force in France, with complete recovery from the nephritis.

(ii) RESPIRATORY SYMPTOMS:-

Respiratory symptoms may occur in association

with any of the cerebral manifestations already described, and there is reason to believe that in many cases they are of central origin. It must be remembered, however, that dyspnoea also occurs as the result of gradual failure of the circulation, or because of interference with the working capacity of the lungs, and it may also occur as the sole "uraemic" manifestation.

The chief respiratory manifestation is dyspnoea, which may be of various characteristic types and degrees of severity. It may be continuous, paroxysmal, or of the Cheyne-Stokes type. The more severe paroxysms tend to be associated with the acute cerebral manifestations, and are believed to be most common with scarlatinal nephritis and granular kidney. The less severe paroxysms, and the Cheyne-Stokes respiration tend to occur with the more chronic comatose state.

The paroxysmal dyspnoea has several features in common with "Asthma" and has been termed "Uraemic Asthma" - a phrase which is to be deprecated. The attacks are sudden in onset, and are apt to occur at night. The dyspnoea may be expiratory like asthma, or inspiratory, resembling laryngeal stenosis; or again, both inspiration and expiration may be free, but unnaturally hurried. Attacks are frequently accompanied by sibilant râles, but do not ordinarily

yield to any of the usual remedies for asthma, while relief is sometimes afforded by measures calculated to remove nitrogenous waste material.

The dyspnoea may be the only sign present, even in fatal cases, and in the asthmatic type the patients are suddenly seized with a severe paroxysm, sitting up and gasping for breath. The breathing is noisy, hissing and asthmatic in character, there is frequently no great lividity, and the patient not uncommonly is conscious and his mind clear. These attacks much resemble the paroxysms sometimes seen in leukaemia.[21] A frequent characteristic is the hissing dyspnoea described by Addison, and Rose Bradford[22] has drawn attention to the marked similarity between this type and the breathing seen after excessive doses of salicylates. The dyspnoea is associated with a fall in the CO_2 of the alveolar air from the normal 5 per cent. to 3 per cent. or even lower, and there is a diminished alkalinity of the blood, from the presence of some non-volatile acid.

Stomatitis is a common accompaniment and Rose Bradford[23] affirms that the combination of dyspnoea of a hissing character, in a drowsy patient with bleeding gums, is very typical of the "uraemic" state.

At first there may be no signs in the chest except the usual cardio-vascular signs of chronic nephritis, but as the attack proceeds there are

usually abundant moist sounds from the development of oedema of the lungs. The heart fails, the patient becomes steadily waterlogged, slipping down into the bed from the orthopnoeic position as he becomes more and more drowsy. The fatal issue may not occur in this way, however, copious pleural effusions frequently being the precursors of acute cerebral symptoms during their rapid re-absorption.

Less common than this paroxysmal dyspnoea is Cheyne-Stokes respiration. The periodicity may affect other functions besides the respiratory, and in a well-marked case the following phenomena occur:- "With the waxing and waning of the respiratory rhythm the pulse rate is altered in such a way that the rate is quickened with the noisy breathing, and slows down again during the period of apnoea; the periodic variations in the pulse rate are not quite synchronous with the periods of respiratory rhythm; there is, so to speak, some slight over-lapping; the pupil contracts and dilates, the dilatation occurring with the noisy breathing or just preceding it, and further, during the period of noisy breathing the patient is restless, subject to irregular muscular movements until during the apnoeic period he gives way to complete temporary coma." (J. Rose Bradford).[24.]

These phenomena suggest that Cheyne-Stokes breathing is something more than a mere periodicity of the rhythm of the respiratory centre, and many other functions of the nervous system are simultaneously affected. In some cases in which Cheyne-Stokes breathing is seen the patient is not completely unconscious, and a waxing and waning of consciousness may be observed; but this is a rare phenomenon in comparison with the others described above. Cheyne-Stokes breathing is more common with chronic manifestations than with the more acute symptoms.

Although the above association of symptoms with Cheyne-Stokes respiration is usually described as occurring in "Uraemia," it is not strictly limited to this condition. I have myself observed a similar periodicity in the whole of the cerebral functions in combination with the Cheyne-Stokes type of breathing, in a case of secondary heart failure due to obstruction of the circulation by primary malignant disease of the lungs.

(iii) GASTRO-INTESTINAL SYMPTOMS:-

The gastro-intestinal symptoms are very constant and tend to be very persistent. Nausea, hiccough, vomiting and diarrhoea constitute the main manifestations, and the gastric part of these

symptoms may be very chronic, and may for a long time be treated as simple dyspepsia. There is, however, one significant point; the dyspepsia may improve under treatment whilst the vomiting persists. In simple dyspepsia vomiting is never the last symptom to be relieved. The vomiting is usually described as incapable of being traced to any error of diet, and bearing no relation to meals, though Langdon Brown[25] states that this is far from being invariably true, as vomiting may only occur then, and be very misleading. It frequently occurs in the early morning before food has been taken, and in severe cases it may be very frequent and quite uncontrollable. The vomiting affords no relief, and the vomited matter may consist of either acid fluid, or alkaline fluid with an ammoniacal odour. Urea has been detected in this fluid, and the alkaline reaction has been attributed to its transformation into ammonium carbonate.

As in the case of other symptoms this vomiting may be of central origin, though other explanations are, that the ammonium carbonate irritates the stomach; or according to Bartels,[26] oedema of the stomach walls.

Persistent hiccough is another distressing symptom in severe cases tending towards a fatal termination. It has been observed in numerous cases

of chronic interstitial nephritis, and extravasation of urine. Although hiccough is generally regarded as a late symptom, it has occasionally been noted early, and Wagner[27] mentions one instance of chronic Bright's disease in which hiccough and slight oedema of the lower limbs were the sole symptoms.

Diarrhoea is a very common symptom, but there are good grounds for believing that it is not strictly "uraemic" in origin. It is generally a late symptom, and is said to be most troublesome during the night, when six or more watery stools may be passed, though during the day there may have been only one or two actions of the bowels. Such attacks are not in themselves significant of uraemia. Ulceration is present in the bowel, and has been ascribed to irritation by the additional nitrogenous excretion into the bowel which occurs when urinary elimination is inadequate, or to haemorrhages which occur here, as elsewhere, in chronic nephritis, and which may be the precursors of the ulceration. There may also be an intense catarrhal or even diphtheritic colitis. Here therefore, there are local lesions sufficient to account for the symptoms; it is accordingly inadvisable to call these symptoms "Uraemic" as is generally done. At least, the term should be confined to those violent choleraic attacks which are out of all proportion to the local lesions.

After the persistence of these gastro-intestinal symptoms for days, weeks or months, the case usually develops into one or other of the types already described. Thus, certain nervous symptoms may ensue, particularly cramps in the legs, muscular twitchings, contraction of the pupils, occasional and inconstant delirium and gradually increasing dyspnoea - possibly of the Cheyne-Stokes variety, but more particularly characterised by its peculiar hissing quality. The delirium gradually gives way to drowsiness and coma, and the patient dies from failure of respiration, sometimes gradually, sometimes with remarkable suddenness.

Many other symptoms have been described by various writers, and attributed to the "uraemic" state. Thus, skin lesions have often been observed and it is possible that some of the eruptions are primarily due to central nervous changes; those observed most commonly occur as bright red maculae or papulae upon the extensor surfaces of the forearms and legs, spreading rapidly over the whole body, or they may appear as a generalised erythematous, scarlatiniform, papular or vesicular eruption. The eruptions occasionally become eczematous and are frequently accompanied by severe itching.

Bromidrosis, or foul smelling sweating may occur, sometimes associated with hyperidrosis, though more

usually sweating is diminished. The foul smell of the sweat is not characteristic of "uraemia" and is said to be due to the growth of the Bacillus Foetidus upon the sweat after exudation.[28]

Uridrosis, in which urinary constituents are present in the sweat in abnormal quantity also occurs; it is quite unmistakable, the sweat has a urinous odour, and gives an effervescent reaction with sodium hypobromite. In its extreme form it occurs as "urea frost." This is a very rare condition first described by Schottin[29] in 1852, from observations on cholera patients. In 1876 Taylor[30] described a case of a patient with Bright's disease, in whom, two days before death, white masses of crystalline spiculae and prisms appeared on the face, neck and hands, which yielded the several reactions of urea. The patient's face is described as having looked as though flour had been sprinkled over it. According to Fagge,[31] the condition only appears shortly before death, and scarcely ever unless the urine is completely suppressed.

Stomatitis is a very frequent symptom, as has already been mentioned, but, a special "Uraemic Stomatitis" has been described by Barié,[32] in which the mucosa of the lips, gums and tongue becomes swollen and erythematous. The saliva may be increased, and there is difficulty in swallowing and mastication.

The tongue is usually very foul and the breath foetid.

In acute cases simulating gross lesions of the brain Babinski's extensor planter reflex may be present. Typical Jacksonian Epilepsy has been described.[33] According to O'Hare, generalised convulsions are less commonly seen nowadays than formerly.[34]

Of Respiratory symptoms, Bradypnoea is an exceptional manifestation, though in some cases of coma it may be pronounced.[35]

Terminal infections are very frequent, and of these pericarditis and pleurisy are the commonest. Peritonitis and Endocarditis have also been described, and, more rarely, Meningitis.

Marshall[36] has recently emphasised the special tendency of "uraemics" to bleed, and states that it may be the most striking symptom. He describes two cases, in one of which haemoptysis was the outstanding feature, with further bleeding after passage of of catheter and stomach tube. This patient died in coma. The second case was admitted to hospital for bleeding from the mouth and the umbilicus, she had no haemorrhages into the tissues. She became comatose and died. The diagnosis of granular contracted kidney was established at autopsy.

To conclude this part of the description of the symptomatology, I propose, by way of illustration, to describe a case which was recently under my care, and

which I had the opportunity of following to its ultimate conclusion.

The patient was a Mr. M., aged 40 years. The relevant history commences in 1912 when he contracted syphilis. His previous health had been good. He consulted his doctor and received one massive intravenous injection of 606. His symptoms disappeared and he remained perfectly well. In May 1920 he again consulted his doctor entirely as a precautionary measure. He had no complaints. He was found to have a strongly positive blood Wassermann. His urine at that time contained no albumin and no sugar. He was treated by weekly injections of Galyl from May to September receiving in all 2.75 Gms., and with Mercury Cream of which he received 8 grs. On 20th December 1920 his urine was free from albumin.

During the late summer or early autumn 1927 he had observed a gradual swelling of the scrotum. He sought advice regarding this swelling on the 22nd November 1927, when he first came under my care, and he continued under my direct observation from that date until his death, except for a period March-August 1928 when he failed to report, but was leading an active life. He was found to have a hydrocele, and an induration and enlargement of the right testis. His urine at this time was found to contain a fair amount of albumin. Granular and hyaline casts were

present in the centrifuged deposit. There were no other indications of disease of the genito-urinary tract. His prostate and seminal vesicles were healthy, and his kidneys not palpable. The hydrocele was aspirated, and the fluid, on laboratory examination, was reported as "marked positive" Wassermann.

He received weekly intravenous injections of N.A.B., with a rest week every fortnight, from 29th November, 1927 until 29th February, 1928, receiving 6 Gms. in all, and in addition 5 grains of potassium iodide thrice daily in a mixture.

The hydrocele did not recur, and the testicular swelling, presumably a gumma, rapidly subsided. He had no subjective phenomena at this time.

His urine was regularly examined and albumin was constantly present with occasional granular and hyaline casts. Estimations by Esbach's albuminometer were frequently made with results such as the following:-

6th December, 1927	=	0.05 per cent. albumin.
10th January, 1928.	=	0.1 " " "
25th " "	=	0.05 " " "
1st February, "	=	0.06-0.07 " "

By the end of February he was free from symptoms, and left the town for a holiday. He was told to report at frequent intervals, but failed to do so.

His next complaint was made on the 14th September 1928. He told me he had been keeping well, but

complained of a large swelling in the mouth which had come on suddenly and caused severe dyspnoea and choking. I found the swelling to be a large haemorrhagic bulla 1" by ¾" reaching from the junction of the hard and soft palates to the root of the uvula, almost filling the mouth and seriously interfering with the respiration. This was incised, and a large quantity of blood removed, with complete relief of the symptoms. On inquiry he told me that for some time previously he had been subject to blood blisters, especially on the lips, and that he "bled easily." (This is an interesting comparison with the cases described by Dr. Marshall). He made no other complaint, but the urinary findings were as before, and it was noticed that he appeared a little pale, and his face somewhat oedematous, especially round the eyes.

He was treated, and remained well up to the 3rd December, 1928, when he complained of vague sensations in the head, night starts and giddiness. He was very worried and depressed. On 27th December, 1928 he made his first tangible complaint. He stated that for about 10 days previously he had noticed a dimness and blurriness of vision. His sight was tested and found to be R 6/60, L 6/24. Both pupils were dilated and reacted sluggishly to light, especially the right. There was no contraction of

the visual fields, and no interference with the movements of the external ocular muscles. He had a pulse rate of 116. His retinae were inspected and he was found to have a marked degree of albuminuric neuro-retinitis; this diagnosis was confirmed by an ophthalmologist. His urine contained 0.06 per cent. albumin.

On the 1st January, 1929 the dizziness previously mentioned returned and he took to his bed. He had an epistaxis, which was, however, easily controlled. His total 24 hours quantity of urine at this time was 1½ pints. The Urea Concentration test gave an estimate of 0.8 per cent. urea. His blood pressure was 180 Systolic - 120 Diastolic.

During the next two or three days he developed gastro-intestinal symptoms and vomited everything swallowed. His face became pale and oedematous, and insomnia was a marked feature. On 6th January, 1929 the vomiting improved, his pulse was 88 and his temperature 99°. He passed a restless night, and on the day following complained of a slight substernal discomfort, his pulse was 98, and his temperature 98.8°. A soft systolic murmur was heard at the apex. His urine quantity in the 24 hours was a little less than 1½ pints. He had developed some more of the blood blisters previously mentioned on his lower lip.

In the afternoon of this day pericardial friction became evident.

On the following day his pulse was 125 and his temperature 97°. A very loud to and fro pericardial friction rub was heard over the whole praecordia. Insomnia was still very obstinate, and vomiting had recurred and was very troublesome. His skin was dry, and his tongue dry and brown.

During the night he slept a little, an ice-bag having eased his praecordial pain. The next day his pulse was 104; his bowels moved several times; pericardial friction was very loud, and the whole of the lower lobe of the left lung was consolidated, and loud tubular breathing was to be heard. He had only passed 2 ounces of urine in the 24 hours.

During the next two days he obtained some relief from his symptoms. On the 11th January, 1929 it was found that he had passed no urine. Percussion indicated a distended bladder and a catheter was passed and 45 ounces of urine removed. Albumin was estimated as over 0.1 per cent.

On the 12th January, 1929 he ceased to complain of pain, and became very drowsy until he lay in a semi-comatose state, only rousing when addressed vigorously. His pulse was 96 and his temperature 96°. He had no dyspnoea, but there was no evident change in the pulmonary or pericardial signs. Dur-

ing the day he commenced to hiccough.

During the night of the 12th January, 1929 occasional twitches occurred in the arms. On the 13th January, 1929 he had no vomiting, hiccoughing was severe, râles were to be heard all over his chest, and his temperature would not register on the thermometer. He was conscious only on rousing. At 12-30 p.m. he had a tonic-clonic epileptiform fit lasting about 2 minutes. After the fit he lay comatose with stertorous breathing and contracted pupils. At 5-30 p.m. he had a second attack of convulsions, and a third at 2-30 a.m. in the morning of the 14th January, 1929, at the height of which he died.

SYMPTOMS OF "ANEPHREXIA."

The first complete account of the symptoms which arise as the result of the total suppression of the urine, the kidneys themselves showing no marked indications of disease, was made by Sir William Roberts.[37] He made his observations upon cases of "calculous suppression" - that is, where bilateral calculous disease has led to the complete destruction of one kidney, and then the ureter of the sole remaining kidney becomes suddenly obstructed, - and for some time the syndrome was believed to occur only with this condition. It is now known that the symptoms may occur with any case in which both ureters become simultaneously obstructed, from whatever cause, or, more commonly when one ureter

becomes obstructed, and the other kidney has previously been rendered inactive. Rose Bradford records a case in which a precisely similar state resulted where "owing to endarteritis and thrombosis of the interlobular arteries of both kidneys, the renal secretion was practically arrested, and the patient lived for seven days without secreting any urine."[38.]

The condition has an important bearing upon the Retention Theory of "uraemia." The symptoms are those which occur when there is complete retention of all the urinary constituents, yet they present most striking differences from those already described as occurring when there is a partial interference with the functioning of the kidneys by disease. The manifestations are remarkable for their slight intensity, and the patient may live seven, ten or even more days without excreting any urine, and all the so-called "uraemic" symptoms are conspicuous by their absence.

When such a suppression occurs, the patient experiences no obviously severe symptoms for seven or eight days, and it may be difficult for both him and his friends to appreciate the gravity of the condition. He is calm, with unclouded intellect, and pulse, respiration and temperature are natural. The tongue may be clean, and there may be neither nausea

nor vomiting. Soon, however, the muscular strength begins to fail, and there is often marked sleeplessness. There is no desire to micturate, and frequently no urine at all is passed. Usually, however, at very irregular intervals he discharges a few ounces, or sometimes a pint of urine. This is always pale, and of low specific gravity, and unless blood be present it is usually free from albumin. After about a week symptoms appear which are usually followed by a fatal termination within two or three days. Of these, the most characteristic are muscular twitching of the face and forearms, contraction of the pupils and a falling temperature. The muscular weakness rapidly increases, and with involvement of the respiratory muscles the breathing becomes slow and panting. Anorexia is the rule, and the tongue and palate become dry. Towards the end progressive drowsiness occurs, with short fitful snatches of sleep, and a mild quiet delirium.

The outstanding negative characteristics are the absence of convulsions, dyspnoea, amaurosis and coma, consciousness being preserved to the last, and cases have been recorded where the patient has spoken sensibly the instant before death. Diarrhoea and severe vomiting very rarely occur. The skin is moist, and there may be profuse sweating. There is never any ammoniacal or urinous odour from the surface of the

skin or with the breath. Oedema is quite exceptional, Fagge[39] records one instance of slight general anasarca when the suppression first took place, but it had passed off entirely by the third day.

According to Roberts the duration of life is, as a rule, from nine to eleven days, and he remarks that the passing of a few ounces, or even of two or three pints, of a dilute urine does not seem to prolong it by more than a few hours. He only knew of three cases in which the patient survived beyond the eleventh day. In one, recorded by Rayer,[40] death did not occur until the twenty-fifth day; in another, recorded by Sir James Paget,[41] death did not occur until the twenty-first day; the third, a patient of Roberts',[42] survived until the fifteenth day. Since then, other writers have recorded similar examples, but such cases are rarities.

The age of the patient appears to have no effect upon the symptoms, nor influence in accelerating or retarding their progress.

Recovery has been known to occur in a few cases in which almost complete suppression had existed for nine or ten days; muscular twitchings had not occurred, but slight mental confusion and contraction of the pupils were present.

PART III.

The Pathological and Biochemical Changes associated with "Uraemia."

Section i.

CHANGES IN THE ORGANS IN "URAEMIA."

As "uraemia" is not a specific entity, and may manifest itself in so many different ways, there are no constant characteristic changes to be found in the organs at post-mortem examination. The most characteristic variations from the normal are the Biochemical changes - especially of the blood, - which have been exhaustively studied of recent years.

In the central nervous system one striking feature often found at autopsy of "uraemics" - and at one time made use of to explain the symptoms - is the "wet-brain," which has been compared with that of acute alcoholism and delirium tremens.[1] The entire cortex of the brain in patients who had died during or after a "uraemic" paroxysm has been found scattered over with large numbers of punctiform haemorrhages (Cohnheim).[2] Chromatolysis of the cortical ganglion cells has also been repeatedly observed. The cerebro-spinal fluid is frequently excessive in amount, and may, during life, be found to be under a heightened pressure.

Definite changes in the liver are unusual in "uraemia," in marked contrast with eclampsia and acute

yellow atrophy, in which they are very prominent.

A catarrhal, and sometimes diphtheritic colitis may be found.

The changes due to terminal infections e.g. pericarditis, pneumonia, are very frequently present, and have often failed to yield bacteria, though pathologically they appear to be toxic processes.[3]

In the kidneys the morbid changes found are those due to the particular condition of which the "uraemic" state was the terminal complication. These conditions have been referred to already in a previous part, and a description of their pathology is not relevant to the subject of this Thesis. In severe renal disease, however, the kidneys suffer an impairment of function of which a brief description may not be out of place at this point.

The observations of Widal and Strauss in 1902 led to the conception that individual functions of the kidneys might be separately impaired. Two great classes were described, (i) "chloride retention," associated with oedema, and (ii) "nitrogen retention," with a tendency to "uraemia." This division was followed by the claim that retention of individual nitrogenous constituents of the urine occurred at different periods. Later, this hypothesis that different functions of the kidney may be individually affected, has been called in question, and Fischberg has recently

published the results of an exhaustive study to maintain the claim that, "no matter what its anatomic substratum, impairment of renal function is manifested by injury to all the excretory functions of the kidney, and that when selective retention occurs in Bright's disease, it is not due to inability of the kidney to excrete the retained substances but to intervention of an extra-renal factor."[4].

Another suggestion advanced to explain why the concentration of certain substances in the blood is not increased in renal insufficiency is, that whilst there is actual retention of these substances, they are stored in the tissues and not in the blood. In the case of sodium chloride this hypothesis, by assuming secondary retention of water, has been put forward as an explanation of oedema. As most cases of "uraemia" in chronic Bright's disease are not oedematous, or only show an obviously "cardiac" oedema, it has been suggested by Ambard and Beaujard[5] that sodium chloride may be retained in the tissues without corresponding retention of water ("rétention sèche").

According to Fischberg, neither selective injury to individual functions of the kidney nor extravascular storage in the tissues explains the accumulation of certain substances in the blood in "uraemia," whilst the concentration of others is not increased.

The following three factors will affect the

chemical findings:-

1. The concentration ratios of the individual urinary constituents.

2. The possibilities for extrarenal excretion of the urinary constituents.

3. Variations in the amounts of the urinary constituents brought to the kidneys.

Only the first of these falls within the scope of this section; the others being more suitably dealt with later.

It has been found that the amount of a given substance in the urine is greater than the amount in a similar quantity of blood serum. A concentration of the substance has taken place during its passage through the kidneys. It has been shown by Maclean[6] and others that the normal capacity of the kidneys to produce this concentration is not the same for all substances.

The following table indicates the approximate number of times that the kidney is able to concentrate the different urinary ingredients (Fischberg).[7.]

Substance.	Concen. in blood mg. per cent.	Concen in urine. mg. per cent.	Approx. no. of times concentrated.
Urea.	30	2,000	65
Uric acid.	2	60	30
Creatinin.	2	75	35
Indican.	0.05	1	20
Phosphate.	3	150	50
Sulphate.	4	150	40
Potassium.	20	150	7
Chloride.	350	500	1.5
Sodium.	300	350	1
Calcium.	10	15	1.5
Magnesium.	3	6	2
Water.	..	..	1

Other workers have obtained very similar figures, Maclean[8] giving the following:- Urea concentrated 72 times, uric acid 29 times, creatinin 40 times. Myers[9] gives the figure for creatinin much higher - 100 times, urea 80 times and uric acid 20 times.

One of the most important functions of the kidney, therefore, is a highly selective concentration and elimination of the various constituents found in the blood. In severe renal disease this function is interfered with, and the extent to which the kidneys are able to concentrate various substances has been made the basis of many tests for renal efficiency. It will be shown later that in "uraemia " certain constituents are commonly retained in the blood, and that the substances which accumulate are those which are normally highly concentrated by the kidneys, while the substances which are normal or show only a slight variation in the "uraemic" patient, are normally only slightly concentrated by the kidneys.

The main change, therefore, which interferes with the physiological functioning of the kidneys is an inability to concentrate the various constituents in the urine. For a time this may be compensated for by increased volume, but eventually the kidneys become incapable of elaborating a urine of higher specific gravity than 1010, at which level the osmotic pressure of the urine approaches that of the blood. This state has been termed by von Koranyi, "Isosthenuria."[10].

THE SUPRARENAL GLANDS.

Enlargement of the suprarenal glands in individuals who had died in "uraemia" terminating chronic interstitial nephritis has frequently been recorded, often associated with hyperaemia, and haemorrhages. It was suggested by Schur and Wiesel[11] that this enlargement might be an etiological factor in the production of hypertension. This suggestion has not found much favour. Patients dying from "uraemia" are very subject to secondary infections, and Langlois[12] and Porak[13] have shown that infections of all kinds are likely to cause adrenal enlargement. It is, therefore, difficult to decide in any one case whether the enlargement is the result of the "uraemia," or is brought about by the secondary infections.

To elucidate this problem Mackay and Lockard[14] recently conducted a series of experiments in which the condition of the suprarenal glands was investigated

after the production of experimental "uraemia" in albino rats. They found that the production of "uraemia" by the removal of both kidneys is followed by hypertrophy of the suprarenal glands, the enlargement being as much as 65 per cent. in the case of male rats, and 47 per cent. in the case of female rats. The enlargement is due entirely to hypertrophy of the cortex, the increase in the volume of the cortical tissue amounting to approximately 40 per cent. for males, and 61 per cent. for females, and is due chiefly to an increase in the size of the cells. The content of water and lipoids was higher in the "uraemic" than in the control glands, though after allowing for such storage a true cortical hypertrophy remained, amounting to 21 per cent. Histologically the stainable fat had a more irregular distribution, and was present in lesser amount in the glands of the "uraemic" animals. The capillaries of the medulla and reticular cortex were distended, and the nuclei of both cortical and medullary cells were swollen and stained faintly.

They found no reason to believe that the alterations in the suprarenal glands in "uraemia" are "unique for this condition." Similar changes have been described in other intoxications, and also as a result of the injection of foreign proteins.

The hyperaemia, congestion and oedema, haemorrhages, and necrosis which have been described in

"uraemia," are common to all severe infections and intoxications. (Pfeiffer; Oppenheim; Goldzieher.[15]

METABOLISM.

In 1895, Kornblum[16] stated that nitrogenous metabolism is much impeded in nephritis. Later researches by Levene[17] and others, who made careful metabolic studies in cases of advanced chronic interstitial nephritis, showed that patients with severe renal disease are unable to convert protein into urea as rapidly or completely as can healthy people.

When the blood nitrogen figures are very high there is also an increase in the non-protein nitrogen of the tissues (Foster),[18] which, according to Weiss and Garner,[19] may contain more urea than the blood, and studies of metabolism show nitrogen retention of considerable degree, sometimes over 1 gramme retention when the intake is but 10 grammes per day.[20] According to Becher,[21] although the muscles take up a particularly large proportion of the retained products of metabolism, all tissues hold more or less, for there is no special storage tissue, and the various substances are distributed in the tissues in the same proportion as in the blood. In the body of one person who died from "uraemia" the total retained urea amounted to 200 grammes.

It has been estimated that the Basal Metabolism is somewhat lowered in "uraemia."[22]

THE HEART.

It was observed long ago that the "uraemic" paroxysm is frequently preceded by a short period during which the pulse is often considerably retarded (Cohnheim),[23] and during the attack itself the pulse is frequent, small and even imperceptible to the finger, or can only be felt over the heart and carotids. (Wagner).[24]

According to Lewis,[25] the removal of both kidneys in rabbits produces fatty degeneration of the myocardium.

With the particular view of noting any toxic effects on the heart muscle as shown by the electrocardiograph, Wood and White,[26] in 1925, published the results of a series of observations made on thirty-nine cases of "uraemia" with nitrogen retention. All the cases had a non-protein nitrogen of 69 mg. or over, per 100 c.c. of blood. Twelve cases showed abnormal electrocardiograms suggesting that, "in certain cases of uraemia and severe nephritis with an increased blood nitrogen there is a toxic effect acting in some respects like digitalis on the heart muscle. It may produce changes in the T wave of Lead II, less often abnormal rhythm, and rarely an increase in the auriculo-ventricular conduction interval or in the duration of the QRS complex."

Section ii.

THE BLOOD CHEMISTRY IN "URAEMIA."

It has been known since the early investigations of Bostock, Christison, Babington and Barlow[27] that the blood undergoes certain changes in its composition in severe renal disease. It was established, (1) that the blood often contains urea, sometimes in as high a percentage as is found in the urine, (ii) that the blood serum is apt to be of lower specific gravity, and less albuminous than in the healthy state, (iii) that the quantity of fibrin varies, being diminished in the early stages of the disease, but reverting to the normal proportion later, and (iv) that the blood pigments, and both red and white corpuscles are reduced.

These findings have since been confirmed and amplified by later workers. Erben,[28] who studied the variations in the normal components of the blood during nephritis, found that the total protein was decreased, and that the albumin was reduced in relation to the globulin. This was particularly the case in parenchymatous nephritis. He found the lecithin and calcium also decreased. Similar results were obtained by Rowe[29] who found, in cases of chronic nephritis with oedema, the serum proteins greatly decreased, with an increased globulin proportion; in cases of nephritis with "uraemia," the globulin increased but the total protein content usually normal or even slightly higher;

whilst he found in cases of nephritis without either oedema or "uraemia," a marked increase in the globulin. Parallel results have been obtained by many other workers,[30] and, in general, it has been found that with the nephrotic type of kidney, and often when there is no oedema, the blood proteins are reduced, mainly at the expense of the globulin, whilst with the sclerotic type, if there be no heart failure, the plasma proteins may be normal.

The blood fats and cholesterol have been investigated by Bloor, Hiller and others,[31] and are often found to be increased in amount. This occurs more especially in the nephritis affecting mainly the tubules, or in nephrosis, rather than in those forms which are more commonly associated with "uraemia;" such a nephrosis being associated with marked deposition of cholesterol esters in the kidneys. (Dyke).[32].

Recent researches, however, have been directed chiefly to the study of the contained constituents in the blood, rather than to the study of the blood itself. To the earlier workers very little was known beyond the fact that urea could be found in the blood where in health it was not discoverable. Although during the latter half of the last century many attempts were made to analyse the blood, yet very little reliable information was obtained until recent years. At the beginning of the present century only the non-protein nitrogen, urea and chloride, could be accurately

determined in the small quantities of blood available clinically. Since then, methods have been developed, especially on the Continent and in America, for the estimation of numerous other substances in small volumes of blood. By means of these micro-methods the blood chemistry of "uraemia" has been exhaustively studied.

Amongst the first important steps in the modern advance of the study of the chemistry of the blood were the physico-chemical experiments of von Koranyi,[33] who proved beyond doubt that there is a retention of organic substances in "uraemia." He found that in "uraemia" the Freezing point of the blood is considerably reduced, instead of the normal depression of -0.56° the freezing point is usually lowered to more than -0.60°, and sometimes to as low as -0.76°.[34] At the same time, the Electrical conductivity may not be increased (Bickel),[35] but may even be reduced; as the electrical conductivity depends upon the number of dissociable molecules, chiefly inorganic salts, contained in the blood, it follows that these are not increased.[36] The increased molecular content indicated by the lowering of the freezing point must represent, therefore, an excess of organic molecules, which dissociate little, if at all, and hence do not conduct electricity. These observations were later corroborated by other workers. (Tieken, Butterfield and others).[37]

Some authors have claimed that as a result of the increased molecular content of the blood the osmotic pressure is much increased, and may be responsible for symptoms of "uraemia." This hypothesis was investigated by Strauss,[38] who found that a marked increase in molecular concentration may occur without "uraemia," and that a severe "uraemia" may occur without an increased osmotic pressure of the blood.

The physical researches of von Koranyi were chemically explained when Widal and Strauss[39] demonstrated that the concentration of non-protein nitrogen in the blood is increased in "uraemia," whilst in these cases the chloride content was shown to be normal.

This research was the introduction of the conception of isolated interference with individual functions of the kidneys, and Bright's disease became divided into the two great groups (i) that in which sodium chloride is retained, characterised clinically by oedema and, (ii) that in which nitrogenous products are retained, and showing a tendency to "uraemia." This division has found wide favour, being known in this country and in America as "chloride retaining" and "nitrogen retaining," respectively; in France as "hydropigenic" and "uraemigenic;" and in Germany as "chloruric" and "hypazoturia." It is universally recognised that combinations of these two types are very common. The study of the non-protein nitrogen

concentrations in the blood in the second type has led to the claim that, as the kidney fails, impairment of excretion and consequent accumulation of the individual non-protein nitrogenous constituents takes place at successive periods.[40].

The development of improved methods of analysis of small quantities of blood and other fluids is especially associated with the names of Folin and Wu, Denis, Marshall and van Slyke. Whilst all attempts to isolate toxic substances from the blood and organs of "uraemic" patients, or animals, to explain all the manifestations of "uraemia" have thus far failed, as a result of many such investigations the following findings relevant to the subject of "uraemia" may be taken as established.

NON-PROTEIN NITROGEN OF THE BLOOD.

It has been established that normal blood contains on an average from 25-40 mg. of nitrogen in a noncoagulable form in each 100 c.c. of blood, a rise of about 5 mg. being usual after a meal. About one half of this non-protein nitrogen is in the form of "Urea".[41]. Whenever the renal function is impaired, whether the result of renal disease or circulatory deficiency, the non-protein nitrogen of the blood increases; a rise may also occur when there is excessive tissue destruction independent of renal injury. Usually - though exceptions have been recorded - the

amount of the non-protein nitrogen increases as the renal impairment progresses, and the highest figures are met with in "uraemia." Readings as high as 658 mg. per cent. have been recorded in this condition,[42] though occasionally typical attacks of "uraemia" have been observed without a high non-protein nitrogen in the blood, a reading as low as 28 mg. per cent. having been recorded in a fatal case.[43] A series of 130 cases of chronic interstitial nephritis was studied by Foster,[44] who found the average reading for the non-protein nitrogen of the blood to be 84 mg. per cent., with an average of 135 mg. per cent. in cases in which "convulsive uraemia" occurred. The highest readings are usually obtained in cases of chronic hypertensive nephritis; cases of tubular degeneration, or "nephrosis" showing less marked retention of the nitrogenous products of metabolism.

In cases of "Anuria" urea forms a much larger proportion of the non-protein nitrogen of the blood than in nephritic "uraemia."[45]

Gettler and St. George[46] in America, analysed the blood of 600 cases of nephritis and obtained the following results.

	Normal.	Nephritis.
Non-protein nitrogen.	25-40 mg. %.	40-460 mg. %.
Urea nitrogen.	10-18 " "	20-375 " "
Creatinin.	1-1.3 " "	2-42 " "
Uric acid.	0.5-3.0 " "	3-17 " "
Sugar.	60.110 " "	75-160 " "
Alkali reserve - per cent.	63-80 " "	40-75 " "

Other workers have obtained similar results, and the conclusions may be stated generally that:- all the waste nitrogenous products, non-protein nitrogen, urea, creatinin and uric acid, are increased in the blood in cases of true nephritis. The degree of retention, considered in combination with the efficiency of the heart muscle, is a direct criterion of the severity of the lesion, and has been made the basis of many of the chemical tests of the efficiency of the kidneys.

It has been found that there is no constant relationship between the blood pressure and the blood-nitrogen figure. In 1921 Boyd[47] in Edinburgh made a series of observations comparing the non-protein nitrogen of the blood with the systolic blood pressure and obtained such diverse results as, in one instance, with a non-protein figure of 41, a systolic blood pressure of 220 m.m., and in another, with a non-protein nitrogen figure of 220, a systolic blood pressure of only 88m.m. He found that, although the pressure was usually raised, it furnishes no evidence of renal function. Maclean[48] made a corresponding series of observations, using the urea concentration test as the index of renal impairment and nitrogenous retention, and obtained similar results. Tests of renal function, however, usually show a parallel relation between the excretory power of the kidneys and

the retention of metabolic products in the blood.

Hewlett and others[49] have found that symptoms of "asthenic uraemia" are seldom well marked when the blood urea concentration is under 100 mg. per cent., but are rarely absent when the concentration is higher than 200 mg. per cent.

The Uric Acid content of the blood is increased in "uraemia" from a normal of 2 to 3 mg. per cent., up to 7 to 10 mg. per cent. or even higher.[50]

The Creatinin of the blood increases from 1 to 2 mg. per cent. to 5 to 20 mg. per cent. According to Myers[51] and others, a rise in the creatinin concentration is a particularly sinister sign of serious renal damage, and should the concentration reach 5 mg. per cent. or over the prognosis is extremely grave.

The Amino-acid nitrogen content of the blood, though sometimes much increased may be normal, even with extremely high non-protein nitrogen figures. The normal figure has been estimated as about 7 mg. per cent., and Bock[52] records a case of "uraemia" in which as much as 30 mg. amino-acid nitrogen per 100 c.c. of blood was found. Even higher figures have been reported by Feigl[53] who obtained as much as 125 mg. per cent. in one case, and frequently found 60-85 mg. per cent. in others. The majority of modern workers, however, have found that the amino-nitrogen is practically constant in "uraemia," as in

nearly all other conditions.[54]

Owing to the fact that the kidney is unable to concentrate all the nitrogenous products of metabolism to the same degree, it has been stated by Myers and others that in renal disease there is a retention in the blood first of uric acid, then of urea, and lastly of creatinin. The accumulation of uric acid, therefore, has been claimed as an early indication of renal damage. The investigations of Fischberg[55] suggest that this is not invariably the case, and that isolated increase in the uric acid content of the blood in the presence of normal figures for urea in a patient with hypertension, is not due to renal failure, but is a metabolic phenomenon associated with the increased arterial pressure. It has been shown by Fischberg,[56] that in "uraemic" coma previously high uric acid concentration frequently becomes greatly reduced.

The Ammonia of the blood has not yet had its true values established (Folin).[57] According to Myers[58] there is some doubt as to whether ammonia exists in the blood at all. The exact ammonia concentration has always been a controversial point since the time of von Frerichs, who endeavoured to make use of it in his theory of the etiology of "uraemia," though it is known that the amount of ammonia in the blood of "uraemics" is not so great as in the blood of some diabetics, in whom symptoms of "uraemia" do not occur.

Folin and Denis[59] found only 0.03 to 0.08 mg. ammonia-nitrogen per cent., and Nash and Benedict[60] obtained similarly low figures which were not increased after nephrectomy, although the non-protein nitrogen was very much increased. According to Wells,[61] in view of these results, and the many sources of error in analysis, the figures quoted in the literature on the blood-ammonia cannot be accepted. It may be stated generally, however, that the results of the investigations of the vast majority of workers show no evidence of an increase of ammonia in the blood in "uraemia."

Indican is normally present in the blood in a concentration of about 0.05 mg. per cent. It is often increased in renal disease, and frequently accumulates before there are other evidences of retention. In "uraemia" its concentration may rise to 0.2 mg. per cent., and as much as 2.2 mg. per cent. was found in a case recorded by Hass.[62] Indican, however, is not a toxic factor.[63] According to Fischberg[64] the amount of indican varies greatly according to alterations in the source of supply (intestinal putrefaction), but Baar[65] believes that indican retention is the most accurate indicator of renal impairment, for no matter how much indican is absorbed from the intestine, its concentration in the blood remains constant if the kidneys are functioning normally; whereas, without intestinal putre-

faction, a marked indicanaemia occurs if the kidneys are injured, sometimes even when there is little change in the non-protein nitrogen of the blood. Similar findings and conclusions have been put forward by Becher.[66]

The Bilirubin of the blood is decreased in chronic nephritis according to Bath,[67] but not usually with arteriosclerotic kidneys.

Hippuric Acid may accumulate in the blood when the renal function is impaired according to Snapper and Grunbaum.[68] This is an unexpected finding, as hippuric acid is formed by the kidneys.

Imidazole excretion is considerably reduced in nephritis with nitrogen retention, the amount excreted varying inversely with the severity of the disease.[69]

Residual Nitrogen.- Although in the urine the total nitrogen may be all accounted for by the known nitrogenous constituents, in the blood the known substances do not account for all the non-protein nitrogen. In normal blood about 20 per cent. of the non-protein nitrogen exists in an unidentified form, and has been termed "residual nitrogen." In "uraemia" the amount of this residual nitrogen may be much increased. Possibly the usual steps of normal nitrogenous metabolism are not completed, the accumulation of the end-products "blocking" the reactions; nevertheless, a high blood-urea concentration does not usually

result in an increase of the amino-nitrogen of the blood.[70] Some of the undetermined nitrogen fraction may be hippuric acid, some of it histones (Folin and Berglund),[71] and Jackson has found significant amounts of a nucleotid.[72]

INORGANIC SALTS OF THE BLOOD.

Potassium. The figures of the estimations of potassium in the blood in "uraemia" are usually low. Rumpf[73] found that the organs of nephritic patients contained an excess of potassium, and this was attributed by Blumenfeldt[74] to the defective elimination of potassium salts which he had observed in sufferers from renal disease. Denis and Hobson[75] found normal values in the blood, and this was supported by Rabinowitch[76] and others, who found normal ratios, except in a few cases of advanced "uraemia." Fischberg[77] states that the potassium of the blood is only moderately increased in "uraemia," the highest figures he was able to find recorded in the literature being 36 mg. per 100 c.c. of blood. He gives the normal ratio as 20 mg. per cent. All authorities are agreed, therefore, that there is no appreciable increase of the potassium in the blood in "uraemia," and that in many cases its concentration is within normal limits.

Chlorides. There is no record of any increase in the concentration of the chlorides in the blood in "uraemia." Denis and Hobson[78] obtained normal read-

ings, whilst many authorities have recorded low figures in "uraemia."[79]

Magnesium. There is no record of any variation in the magnesium content of the blood in "uraemia." Most authorities are agreed that the quantities found fall within normal limits.

Sulphates. It is common to find the sulphates of the blood increased in "uraemia." Denis and Hobson have recorded that sulphate retention sometimes reaches thirty times the normal figure of 0.5 mg. per cent. It is one of the earliest substances to be retained in renal insufficiency, and it has been suggested, therefore, that sulphates and uric acid resemble each other in their "selective" retention by diseased kidneys.

Calcium and Phosphates. Most investigators have found marked changes in the calcium and phosphate content of the blood in "uraemia," the proportion of each varying inversely as the other. In impairment of renal function the phosphates tend to be retained early, and their estimation has recently been recommended by de Wesselow[80] as giving more reliable results than those obtained by blood nitrogen estimations. A high phosphate figure indicates an unfavourable prognosis. According to Fischberg,[81] in some cases of azotaemic nephritis the phosphate content of the blood may be increased to more than ten times the normal.

Corresponding to the rise in the phosphate the calcium is usually reduced, and de Wesselow[82] has suggested that the low calcium content of the blood may be responsible for the nervous irritability of "uraemia." The normal figure for the blood phosphate is from 2-4 mg. of P. as phosphates per cent., and for calcium 9-11 mg. calcium per cent. In advanced "uraemia" figures of 12-20 mg. of P. and 4-6 mg. of calcium may be found.[83] In some very rare cases of nephritis, however, instead of being reduced the blood calcium is increased to the point of saturation, and metastatic calcification may result. This has been explained by Hubbard and Wentworth[84] as due to calcium being drawn from the bones to help the deficient alkali reserve.

WATER.

It has been claimed that water is not retained as a direct result of renal insufficiency, but in order to maintain the normal concentration ratio of the chlorides in the tissues. According to Maclean[85] the excretion of water is a function of the kidney, and suffers with other functions in renal disorders. This would lead to a direct retention of water, and indirectly to the retention of chlorides, in order to maintain their equilibrium in the tissues. Although the water largely accumulates in the tissues as "oedema," yet he believes there is a direct retention in the blood also, causing "hydraemia."

PIGMENTS.

Urochromogen retention in the serum has been demonstrated by Becher[86] and others, thus explaining the light colour of the urine even in the absence of polyuria.

Haemoglobin is decreased in amount.

REACTION OF THE BLOOD.

Measurements of the partial pressure of CO_2 in the alveolar air in "uraemia" definitely indicate a certain degree of Acidosis. It appears to be only in advanced nephritis that the acidosis occurs in sufficient degree to cause clinical symptoms, but an acidosis may be an early indication of nephritis, and be demonstrable by the alkali tolerance test when it is not sufficient to affect the alveolar air.[87] The maximum degrees of acidosis found in "uraemia" are about equal to those of diabetic coma.[88] It appears to depend upon the inability of the kidney to excrete acids, and is associated with a phosphataemia and a decreased amount of calcium in the blood. Lewis and Barcroft[89] demonstrated that there is a non-volatile acidosis in uraemic dyspnoea, which apparently could not cause other symptoms. Fischer[90] has suggested that a localised acidosis in the nervous system may cause local oedema, and so explain some of the symptoms of "uraemia." Although a general acidosis is usual

in nephritis and marked in "uraemia," there is no evidence that localised acidosis occurs in the nervous system, and there are no means of testing Fischer's hypothesis.

The acidosis which occurs in nephritis differs markedly from that which occurs in diabetic coma in that there is no excessive excretion of organic acids or ammonia, and there are, in fact, no very striking urinary changes at all, even though the acidosis may be very severe. According to Marriott and Howland[91] there is a very definite increase in the inorganic phosphate of the blood in nephritic acidosis, and often an associated decrease in the acidity of the urine. They attributed the acidosis to a diminished ability on the part of the kidneys to excrete acid phosphates, a very important part of the mechanism for maintaining the neutrality of the blood.

The most severe degree of acidosis is observed in those types of nephritis which are associated with "uraemia." Rieger and Freund[92] measured the acid-binding power of the blood by determining the amount of acid that could be added before agglutination of the corpuscles took place. They found this reduced in glomerulo-nephritis before there was any demonstrable nitrogen retention, or other evidence of kidney disease, whilst in cases of nephrosis, and in conditions dependent upon circulatory changes, this was not the

case.

It is usual to find that the degree of acidosis in renal disease is directly comparable with the degree of impairment in the excretory function of the kidneys, and according to Sellards[93] it does not reach a high grade so long as the power of the kidneys to excrete acid is comparatively efficient. Although the administration of sodium bicarbonate corrects the acidosis, it has little, if any, effect upon the course of the disease, or upon the phosphate content of the blood.

Begun and Munzer[94] consider that a part of the acidosis is due to the decreased formation of ammonia during metabolism. Nash and Benedict, who believe that the ammonia of the urine is formed only in the kidneys when eliminating acids, have suggested that acidosis may result either from (i) decreased ability on the part of the kidneys to excrete acids, so that acid retention occurs, or (ii) diminished capacity on the part of the kidneys to form ammonia, so that other bases are excreted with the urinary acids, with a consequence that the alkali reserve of the blood is depleted.

SOME RECENT OBSERVATIONS AWAITING DEVELOPMENT.

When the renal functions are impaired metabolism must be affected generally, and it has been suggested that products of abnormal metabolism may be respon-

sible for the symptoms of "uraemia." The terminal acidity of the blood, associated with the finding of Albumose in the blood of a nephritic by Schumm,[95] suggests the probability of active autolytic processes taking place in "uraemia." Neuberg and Strauss[96] have found Glycine in considerable quantities (1.5 mille), in the blood serum of a "uraemic" patient, and in the blood of nephrectomised rabbits. Choline, a substitution product of ammonia formed by the breaking down of the complicated fat of the nervous system, has been suggested as the toxic factor;[97] and more recently, Trimethylamine, another substituted ammonia, which is said to cause the urinous odour of the breath, has been investigated by Golla.[98] He found it present in traces in normal blood and urine, but increased tenfold in the blood in "uraemia." He did not find it increased in cases of simple suppression, and in these cases the smell is absent from the breath.

In 1922 Sherwood[99] suggested that the urea retained in the blood might account for the acknowledged susceptibility of "uraemics" to infection, by interfering with the Complement Function. Rockwood and Beeler,[100] in 1924, investigated the complement titre of the blood in 9 cases of "uraemia," and did not find it reduced.

The Glycogen Reaction of the blood, whereby granules of glycogen in the polymorphonuclear cells

are stained by iodine, and which was found to occur in certain disturbances of respiration, bacterial infections and severe anaemias, has been found to give a positive result in "uraemia." It has been found, however, to occur with other toxaemias of metabolic origin e.g., chronic morphinism, malignant cachexia, etc.[101].

Foster[102] in 1915, and again in 1921, published particulars of a Toxic Base which he had found in the blood of "uraemics." He succeeded in isolating the substance from 22 cases with epileptiform symptoms, and he has been unable to find it in other conditions. When injected into guinea-pigs symptoms of muscular twitching appear in a few minutes, to be followed frequently by convulsive seizures, paresis of the hind limbs, or diarrhoea, and the animals pass into a stuporose condition ending in death. Foster also found that this substance forms crystalline salts with platinum and gold. He was unable to produce toxic symptoms by experimenting with the blood of over forty controls.

In 1924 C. H. Andrewes[103] described a Diazo Colour Reaction which he found only in "uraemic" serums. He was investigating van den Bergh's test and noted this colour reaction incidentally. Andrewes obtained a positive reaction in eight cases of "uraemia" with blood ureas ranging from 220 to 650 mg.

per cent. Five other cases of nephritis, with blood ureas of from 40 to 275 mg. per cent., gave negative reactions. Normal serums were negative. In an attempt to trace the cause of this reaction Andrewes excluded urea, uric acid, creatinin and proteins. In the same year Hewitt[104] confirmed Andrewes' observations. He simplified the technique of the test, and found the reaction limited to "uraemia." Hewitt made a tentative suggestion that a cyclic amine such as histamine or tyramine might be responsible. He found that alcoholic extracts of urine sometimes gave a reaction which appeared very similar to that in the blood. The reaction was further investigated in 1925 by Rabinowitch[105] who confirmed its value as a clinical test in cases of retention of waste products due to renal injury. He obtained positive reactions before the creatinine concentration in the blood reached 5 mg. per cent. He reported one case, with an initial positive reaction, that recovered. Becher[106] had previously published observations on the diazo reaction in alkaline solution and described a colour reaction, but his technique differed widely from that of Andrewes, and Harrison and Hewitt after a thorough investigation concluded that Becher's reaction could not have been produced by the substance responsible for Andrewes' reaction. Blotner and Fitz[107] in 1927 confirmed the previous records, and found in addition,

(i) that a high blood urea is not of such serious significance when the reaction is negative, as when it is positive, (ii) the reaction becomes positive in nephrectomised rabbits one or two days after removal of the kidneys, (iii) the serum from a nephrectomised dog with a positive Andrewes' reaction is not toxic when injected into rabbits, and (iv) the ascitic fluid of a human patient gave a positive reaction. The cerebro-spinal fluid did not. Harrison and Hewitt[108] further investigated the reaction in 1927 and correlated the work of previous workers. They found that (i) "A positive Andrewes' diazo test is only found in uraemia or severe renal insufficiency. A negative reaction, however, does not exclude uraemia. (ii) The unknown substance responsible for the reaction does not appear to pass into the cerebro-spinal fluid, and is either absent from, or present only in minute quantities in, the red blood corpuscles. The blood of uraemics obtained post-mortem often gives the reaction. (iii) Nitrogenous retention always accompanies retention of the substance responsible for the reaction, but urea retention and Andrewes' test do not run strictly in parallel." They claimed that with the simplified technique they described, the reaction becomes a simple clinical test.

Section iii.

THE CHANGES IN THE URINE IN "URAEMIA."

From the time of Richard Bright the urine has been most thoroughly studied in the natural expectation that valuable data regarding the condition of the kidneys would be obtained. Three important facts were soon established, (i) that the quantity of urine tended to vary, and commonly became reduced before the onset of "head symptoms," (ii) that the specific gravity tended to be low, in spite of the presence of albumin, (iii) that albumin was commonly found, frequently in large quantities associated with dropsical cases, but usually in slight amount in those cases in which dropsy was not a feature. According to Sir Thos. Watson, these three facts, "constitute, together and by comparison with each other, a very accurate and trustworthy test of the presence or absence of the renal disease."[109] Although since that time the character of the urine in various diseases has been widely studied, and the original methods of using these findings have undergone considerable changes - for example, the estimation of the specific gravity of the urine has become the basis of Mosenthal's Renal Test Meals[110] - yet these three facts still remain the important tripod which they constituted one hundred years ago.

Although there is a marked alteration in the composition of the urine in renal disease, yet the study of the chemical pathology of the urine in "uraemia" has not been so productive of useful information regarding this state as has the investigation of the blood. The urine is subject to so many variations within the normal that the results of examinations are apt to be fallacious, and any conclusions cannot be other than of a general nature.

Before attempting to estimate the variations in the several constituents of the urine it is necessary to have standardised normal figures, and for this one requires at the very least a standard diet of known protein content, a measured quantity of liquid, and an analysis of an accurate twenty-four hour specimen.

The Total Volume of the urine in "uraemia" tends to vary. It was early pointed out that a marked diminution in the twenty-four hour output commonly preceded convulsive attacks, but it was soon found that every marked reduction in the quantity was not followed by acute symptoms. Similarly, in those cases of chronic interstitial nephritis in which acute "uraemic" symptoms do not occur, the urinary output may be normal, or even increased, and yet the more chronic manifestations of "uraemia" may be present. According to Rowntree and Fitz[111] the actual volume of urine secreted over a given period of time bears little

or no relation to the renal function, although they have constantly observed that the specific gravity is markedly decreased in advanced cases of kidney disease.

Specific Gravity. It is well-known that the maximum specific gravity tends to fall progressively as the kidneys fail, and this has been used as a measure of their functional capacity by means of the "concentration" and "dilution" Tests of Volhard, - the maximum specific gravity being defined as the highest reading obtained during this test. The variations which take place in the specific gravity of the urine in severe renal disease have recently been the subject of an exhaustive study by Fischberg[112] and others. Only cases without oedema were used in their investigations, for in the presence of a subsiding dropsy it is often impossible to ascertain the maximum concentrating power of the kidney, owing to the constant supply of water from the oedematous fluid.

Their results may be summarised as follows:- The lowest point to which the "maximum specific gravity" descended was 1010. Only in isolated instances was it impossible to obtain a specific gravity of 1010 by prolonged deprivation of water, and in these the maximum was either 1008 or 1009.

No case of "chronic uraemia" was found in which the "maximum specific gravity" was not below 1020, and

usually below 1015. In cases of "uraemia" terminating chronic Bright's disease in which the highest specific gravities were between 1015 and 1019, there was always evidence of failure of the myocardium. In patients who exhibited well-marked nitrogen retention without definite myocardial insufficiency, the "maximum specific gravity" was below 1015, and progressed to a terminal inability to achieve a concentration above 1010.

Fischberg[113] also records a case in which he had the opportunity of examining the last 50 c.c. of urine passed by a patient who died of "uraemia," without any signs of myocardial failure - "a purely renal death." The specific gravity was found to be 1010. Autopsy revealed "primarily contracted kidneys complicated by slight bilateral pyonephrosis."

These investigators concluded that the maximal impairment of renal function (apart from total anuria) is characterised by inability of the kidneys to elaborate a urine of a higher specific gravity than 1010.[114].

PROTEIN.

The presence of protein is an almost constant finding in "uraemia," the quantity may be great or small, and at times it may disappear altogether. The smaller amounts are associated with the more chronic "uraemic" symptoms which occur most frequently with chronic interstitial nephritis. In the later stages

of the disease, however, when the heart begins to fail, the amount of protein increases. When considered alone the presence and quantity of protein in the urine is of uncertain value as an indication of renal damage. Many people with quite healthy kidneys may exhibit proteinuria, and conversely renal disease may exist without proteinuria. In accordance with the finding that in the blood the protein depletion is mainly at the expense of the albumin, it is usual to find that of the protein in the urine the albumin exceeds the globulin in the proportion of 6 to 1, a distinctive feature, according to Mackenzie Wallis,[115] of an inflammatory lesion of the kidneys; the ratio with degenerative changes being 2 to 1.

TOTAL NITROGEN.

Although protein is generally found in the urine in "uraemia" in varying amounts, the total nitrogen percentage is considerably reduced. This is associated with a reduction in the urine of the various nitrogenous constituents. The fact that the concentrating power of the kidneys for urea is impaired in renal disease has been made use of by Maclean[116] as the basis of his well-known "urea concentration test." Using this test, Fischberg[117] compared the power of the kidneys to concentrate urea with the "maximum specific gravities" obtained in a series of "urinary concentration" tests. He found that patients with maximum impairment of concentration, i.e., with a "maximum

specific gravity" of 1010, cannot elaborate urine containing more than 0.9 per cent. of urea, and the maximum is usually less. Under similar conditions the normal kidney readily concentrates urea to over 2 per cent.

The other nitrogenous constituents, uric acid, creatinin and purins, are all similarly reduced in the urine in "uraemia," though not all to the same extent, owing to the different concentrating powers of the kidneys for different substances.

In all forms of renal disease the Ammonia content of the urine may be found to be increased. According to von Noorden[118] the rise above the normal average of 3 to 5 per cent. of the total nitrogen is only relative, and is caused by the diminution of the total nitrogen, such as the urea, rather than an actual increase of the ammonia, which is one of the substances easily excreted by the kidneys. It is only in cases of "uraemia" that the ammonia tends to increase absolutely as well as relatively. The increase is not great, however, and the total quantity is usually less than 1 gramme daily.

INORGANIC SALTS.

The excretion of salts in "uraemia" is subject to great variations. In chronic conditions especially, retention may occur followed by copious compensatory excretion.

The Phosphates are usually decreased in amount, and Fleischer[119] found that in several cases of chronic interstitial nephritis the excretion of phosphoric acid diminished when the excretion of urea was lowered, but also in some cases in which the urea excretion was normal. The so-called relative phosphoric acid value - 100 P_2O_5 : N - was always remarkably low. Fleischer concluded that diseased kidneys excrete phosphates with great difficulty. Their retention in the blood and its significance has already been described.

The Sulphates of the urine are reduced in "uraemia," the variations tending to run parallel to those of the nitrogen,[120] though exceptions to this rule have been recorded.[121].

The Potassium of the urine was for a long time considered to be responsible for "uraemic" symptoms. Soetbeer,[122] who made observations on the excretion of potassium in renal disease, records two cases, one of granular kidney and one of acute nephritis. In both cases "uraemic" symptoms were present, but the output of potassium was equal to the intake..

The Calcium concentration in the urine in impaired renal function has recently been the subject of an investigation by Hétényi and Nógrádi.[123] These workers found that the capacity of the kidneys to concentrate calcium is greatly diminished when renal function is impaired. In spite of this the calcium, as

in the case of chloride, is not retained in the blood, and, in fact, is commonly diminished, as has been already stated. This is probably due in part to the facts that, normally calcium is but slightly concentrated by the kidneys, and is excreted by the intestine in probably larger quantities than by the kidneys.

The Chlorides are the most important of the urinary salts. The maximum concentration of chlorides in the urine of patients with impaired renal function is more difficult to ascertain than that of urea, because of the frequent complication by myocardial insufficiency, which greatly reduces the concentration of chlorides in the urine, even though the kidney function be normal. Fischberg,[124] who made a similar comparison between the "maximum specific gravity" and the chloride concentration as he did with the concentration of urea, found that in cases of maximum renal insufficiency the highest chloride concentration is always a low figure; the highest he obtained was 0.42 per cent., - calculated as sodium chloride - and in many cases the concentration was much lower. Under similar conditions the normal kidney excretes a urine containing over 1 per cent. and often 1.5 per cent. of sodium chloride.

According to de Wesselow,[125] "the kidney in interstitial nephritis shows, when examined by a

chloride concentration test, an inability to concentrate chlorides running parallel with the failure of capacity to concentrate urea."

Although, as has been already described, this impairment of the ability of the kidney to concentrate chloride is not usually associated with its retention in the blood in "uraemia," Veil[126] has shown that retention, with a marked rise in the concentration of chloride in the blood, may be produced in renal insufficiency by the ingestion of excessive amounts of chloride.

URINARY PIGMENTS.

The pigments of the urine, Urochromogen, Urobilinogen, etc., are decreased in "uraemia" and are associated with a true retention in the blood.[127]

A Recent Observation awaiting Confirmation has been made by Hartmann.[128] He suggested that the substance which causes the characteristic odour of the urine may be responsible for some of the symptoms of "uraemia." He has isolated and described this substance under the name of "Urinod," and believes it to be a cyclic ketone with the empirical formula C_6H_8O. This substance is highly toxic, and causes mental symptoms.

Section iv.

CHANGES IN OTHER SECRETIONS AND EXCRETIONS IN "URAEMIA."

THE SALIVA.

The quantity of saliva secreted in "uraemia" is variable. Ptyalism and stomatitis may occur as definite symptoms due, according to Barié,[129] to the retention and poisonous action of an as yet unidentified body which irritiates the salivary glands.

Jawein[130] has stated that the amount of saliva and the quantity of its diastatic ferment may be diminished. Although this may be so, according to von Noorden,[131] who conducted daily observations upon a series of cases, the exceptions are too numerous to permit of a general statement.

von Noorden and Dapper[132] found, as the result of a systematic series of observations, that the saliva of patients suffering from severe renal disease often, though not invariably, yields a negative or only very slight sulphocyanide reaction. They were unable to establish any constant relation between its presence and the severity of the disease.

Urea may be found in the saliva in "uraemia." Its presence was first demonstrated by Pettenkofer,[133] and subsequently confirmed by many other workers (e.g., Fleischer; v. Noorden; v. Zezschwits; Ritter).[134] According to Fleischer[135] it is not a constant finding, and in any case the amount is small; the greatest

daily amount he obtained - under the influence of pilocarpine - being 0.3 to 0.4 grammes. Out of forty five cases of severe nephritis investigated, urea was found in thirty-eight. Of these, it was invariably present in cases of "uraemia." von Noorden[136] records similar results, but obtained slightly higher estimations.

Uric Acid has been frequently found in the saliva in "uraemia." It is not constantly present. Its presence was first described by Boucheron,[137] who found that it is only present between meals, and is not secreted by the salivary glands during mastication. This observation has been confirmed by von Noorden.[138]

The Molecular Concentration of the saliva in cases of severe renal disease has been investigated by Strauss[139] by cryoscopy. He found that the lowering of the freezing point (-0.18° to -0.29°) was within normal limits (-0.07° to -0.35°).

GASTRIC SECRETIONS.

According to Biernacki[140] the secretion of Hydrochloric Acid and the production of Rennin and Pepsin are very considerably diminished in renal disease. von Jaksch[141] also found a deficiency of hydrochloric acid. Other workers (von Noorden; Krawkow; Dapper)[142] have found the results of investigations very variable. Dapper investigated a series of fifteen cases and found an absence of

hydrochloric acid in three, a diminution (less than 20 c.c. of $^{n}/_{10}$ alkali to 100 c.c. of gastric juice) in seven, and a normal figure in each of the remaining five cases.

Vierhuff[143] and Wagner,[144] also record cases of achylia gastrica in sufferers from severe renal disease.

Urea has been found in the vomited matter in cases of "uraemia," and also in the food withdrawn from the stomach. Although some of the urea thus found might be due to swallowed saliva, von Noorden found that this did not necessarily occur, as he was unable to prove to his satisfaction the presence of urea in food vomited or withdrawn, although in the same case it was present in the saliva. Langdon Brown[143] states that urea has been found in the vomit in greater concentration than in the blood of the same case, and Canti[146] records finding the blood urea of a "uraemic" patient to be 0.3 per cent., whilst the urea in the matter vomited by the same patient was 0.6 per cent.

Ammonia has been found in the gastric contents of "uraemic" patients by Leos,[147] who obtained as much as 0.017 per cent. ammonia. This observation has been confirmed by von Noorden.[148]

FAECES

The thorough investigation of the Faeces in severe renal disease was first undertaken by von

Noorden and Ritter,[149] and their findings have since been confirmed by other workers. The main change was in the excretion of nitrogenous substances, which they found greater than normal, both as regards its absolute amount, and relatively to the nitrogen of the food. The increased quantity of nitrogen excreted is not allied to any special form of renal disease, or to the occurrence of "uraemia," but they found the largest amount excreted - more than three grammes of nitrogen daily - in cases associated with diarrhoea, e.g., "uraemic diarrhoea." In such cases the daily evacuations frequently contain five or six grammes of nitrogen. von Noorden[150] states that it is possible to excrete as much as 8 grammes nitrogen daily through the bowel. The substances constituting the faecal nitrogen are as yet undetermined, but an unusually large amount of Ammonia Salts is frequently present in the diarrhoeic stools of "uraemia." It may constitute from 10 to 20 per cent. or more of the total faecal nitrogen.

THE SWEAT.

The amount of sweat is usually diminished in "uraemic" cases, and the skin is dry. Systematic analyses of the sweat in severe renal disease were conducted by von Noorden,[151] the sweating being artificially induced by the injection of pilocarpine. He found that an examination of the perspiration taken

from different parts of the body showed variations in the amount of contained Urea. This finding is not, however, peculiar to "uraemia." Urea has also been found in the sweat by many other workers, though the amount is usually small. According to von Noorden 3 grammes nitrogen is the maximum that can be eliminated daily through the skin. The percentage of urea in the sweat in "uraemia" is usually greater than in the saliva. In very rare instances it may be deposited upon the skin as "urea frost," a condition first observed in cholera cases by Schottin.

Uric acid, according to von Noorden, in slight traces, is a normal constituent of the sweat.

Ammonia salts, are found in the skin and mucous membranes in severe renal disease, and especially in "uraemia."[152].

THE CEREBRO-SPINAL FLUID.

In cases of "uraemia" with convulsions, the cerebro-spinal fluid has been found to be under pressure, and at autopsies it has often been found in excessive amount.[153].

The Residual Nitrogen is increased in the cerebro-spinal fluid in cases of "uraemia," figures as high as 60 to 80 per cent. of those of the blood being commonly found. (Brun).[154].

Urea. - The interesting fact has recently been brought out that "uraemia" is always associated

with a rise in the urea percentage in the cerebro-spinal fluid. Canti[155] has been conducting a series of researches respecting this fact. His complete results are as yet unpublished, but he has established the following facts:- About 300 observations were conducted by the hypobromite method. He found the distribution of urea in the various body fluids e.g., the blood, cerebro-spinal fluid, pleural effusion, pericardial effusion, ascitic fluid and oedema fluid obtained by Southey's tubes, to be always approximately uniform in any one case. An experiment was devised to demonstrate the rate at which equilibrium takes place. It was found that the urea of the cerebro-spinal fluid established an equilibrium with that of the blood in the course of a very few minutes. Observations on the cerebro-spinal fluid may be taken, therefore, as indicating the general urea concentration in the tissue fluids. Normally this is 0.02 to 0.05 per cent., though this figure may rise when death is approaching. To eliminate this factor, Canti only accepted figures above 0.2 per cent. as indicating definite urea retention. Of ninety-six cases in which "uraemia" was definitely diagnosed clinically, sixty showed urea retention, and thirty-six did not. Serious urea retention was seldom found in cases which recovered, but all cases with a urea content of 0.3 per cent., or more in the cerebro-

spinal fluid were fatal. The highest figure obtained was 0.88 per cent. Of the cases diagnosed as "uraemia" in chronic nephritis two classes could be distinguished. The first and larger class showed urea retention, and all were fatal. The second showed no retention, and some recovered for the time being, and the fatal cases showed cerebral lesions such as haemorrhages, embolism, or thrombosis. Cases diagnosed as "uraemia" with the arteriosclerotic type of kidney also fell into two classes. Of these, the first class, with urea retention, was the smaller, and the retention was not extreme, being rarely above 0.3 per cent., but all were fatal. The second and larger class showed no urea retention and some survived for the time being.

Commenting upon these findings, Langdon Brown[156] pointed out that, as the hypobromite method was used, the estimations included nitrogenous bodies other than urea, and that it would be more accurate to refer to a rise in the non-protein nitrogen, and whilst the urea might be the most abundant constituent it need not be the toxic one. Canti compared the results obtained by the hypobromite method with those given by the urease method. In one case he obtained the following figures:- The blood urea by the urease test was 0.4 per cent. The urea of the cerebro-spinal fluid by the hypobromite method was 0.69 per cent., and by the

urease method 0.45 per cent. The residual nitrogen was, therefore, greatly raised being 0.24 per cent., or expressed proportionately, nearly 35 per cent. of the total, instead of the normal average of about 8 per cent. Similar figures were found in other cases.

DROPSICAL FLUIDS AND EFFUSIONS.

Actual retention of urea in nephritis is usually associated with its solution in oedematous exudates and effusions.[157].

It has been suggested, owing to the frequent occurrence of "uraemic" symptoms during the rapid disappearance of renal dropsy, that certain Toxic Alkaloids or Ptomaines become stored up in the dropsical fluid.[158] None have been demonstrated, however, and according to Carter, the occurrence of symptoms under these circumstances may be due to a progressively diminished alkalinity, or perhaps actual acidity of the blood. To support this contention he states that although under ordinary circumstances, subcutaneous effusions are alkaline or neutral, in Bright's disease they are frequently acid.[159].

NOSE, PHARYNX AND BRONCHI.

The breath in "uraemia" frequently has a urinous odour due, it is believed, to the presence of trimethylamine.

Ammonia may be demonstrated in the breath, but it is not characteristic of "uraemia," occurring, as it does, in all "typhoid" states, originating from

decomposition within the mouth and not exhalation from the lungs.

The secretions of the nose, pharynx and bronchi have been found to contain urea.

Urea has also been found in the milk, which even in health may contain traces.[160].

Section v.

SOME RECENT OBSERVATIONS NOT REFERABLE TO ANY OF THE PREVIOUS SECTIONS.

To study properly the relation of "uraemia" to retained products of metabolism it is not sufficient to determine experimentally the toxicities of these substances under transitory conditions, which are entirely dissimilar to the actual conditions in "uraemia." It is essential to make observations of the effects of these substances when maintained in the organism for long periods at the concentrations occurring in "uraemics." A start in this direction has been made by Hewlett, Gilbert and Wickett,[161] who made observations to determine the effects of high concentrations of urea in the blood of human beings. Large doses (100-125 gm.) of urea were given to healthy men, and it was found that symptoms occurred comparable to those of "asthenic uraemia." These manifestations did not appear until the urea concentration in the blood had reached levels of from 160-245 mg. per cent. - just the concentrations that are usually found in "uraemia." These experiments were of brief duration, and one might reasonably expect striking results if these same concentrations were maintained for weeks at a time.

In chronic diseases experimental investigations must be of some reasonably comparable duration. Methods designed to make this principle of investiga-

tion possible have been devised by Woodyatt,[162] and Leiter[163] has recently endeavoured to determine the effects of urea retention in chronic renal disease by means of an experiment of long duration. He found that the slow injection of pure urea into dogs does produce a train of symptoms strikingly similar to "convulsive uraemia" in man. Leiter also found evidence that when excessive amounts of urea are present in the blood, it is actively excreted by the stomach, bile and intestine, and may produce symptoms similar to "uraemic" colitis in man.

In 1923 Adolf Hermannsdorfer[164] investigating the pathogenesis of "uraemia" and eclampsia, conducted a series of experiments upon normal and parabiotic rats. The parabiosis was established by means of lateral incisions running from the elbow to the knee of the animals, the peritoneal cavities being also put into communication (coelostomy), and having noted the symptoms which resulted - one being that the urine became toxic - he first removed, in stages, three of the four kidneys, with the result that the remaining kidney compensated completely. Blood analyses compared with those made from healthy animals showed no retention of excretory products in the coelostomized animals.

He then carried out a series of experiments to test his theory of a two-fold "uraemia" - (i)"reten-

tion uraemia" due to retention of excretory products (ii) "convulsive uraemia" due to a special poison. His results supported his view. He devised experiments, which, while leaving any possible internal secretion of the kidney intact, allowed the excretory function to be varied at will. The experiments, performed on single rats, consisted in:- (i) Bilateral ligation of the kidney pedicle; (ii) bilateral nephrectomy; (iii) bilateral ligature of the ureters; (iv) removal of the apex of the bladder, the urine becoming absorbed through the peritoneum; (v) injection of urine into the peritoneal cavity. He thus produced the following effects:- In the first four experiments the excretion of urine was hindered; in (ii) by suppressing renal function; in (i) and (iii) by causing marked circulatory and nutritive changes in the kidneys; in (v) the action is similar to (iv) but is more sudden and rapid. The results of all the experiments were identical; death without convulsions in 50 to 70 hours, showing all the symptoms of so-called "retention uraemia" (urinary poisoning).

Having shown that intraperitoneal injection of urine in normal rats produced true "retention uraemia", Hermannsdorfer tested the action of the toxic urine of coelostomized rats in a similar way. The result was death much more rapidly, accompanied by tonic-clonic convulsions similar to those of eclampsia.

Experiments were then devised to discover whether the convulsive poison in the urine of coelostomized rats owed its origin to some alteration of the general metabolism resulting from the union of the animals, or whether the kidneys were especially concerned in its production. This was tested by two experiments:- (1) All four kidneys were removed from the coelostomized animals. The result was "retention uraemia" without convulsions. (2) The apex of the bladder was removed in the coelostomized animals, the kidneys being left intact. The result was death with eclamptic convulsions.

PART IV.

THE MODERN THEORIES OF THE ETIOLOGY OF "URAEMIA."

The earlier conceptions of the etiology of "uraemia" having been already described and discussed, there remain to be considered the more modern views which are under discussion at the present day. To complete this account of the factors concerned in the production of "uraemia" I propose to describe these views, and to state the arguments which have been brought forward to justify them and those which are against them, and to indicate the effect upon them of the most recent researches.

Before proceeding to describe the modern theories of "uraemia" it is necessary to examine the individual symptoms more closely, and to correlate them with the underlying clinical conditions, for the purpose of accurately defining what is meant by the term "Uraemia." This is required because the retention of the term, after its original significance had become obsolete, has allowed so-called "uraemia" to become protean in its clinical manifestations, and, in the words of Langdon Brown[1] "grouping together a large number of symptoms under the term "uraemic syndrome," and trying to find one toxin for them all has tended to obscure the issue and to discourage attempts at detailed correlation of symptoms with their natural causes."

The most constant group of symptoms is the syndrome which has been termed "Latent" or "Asthenic Uraemia" which occurs in cases of suppression of urine, the kidneys themselves showing no obvious signs of disease. I have called this the syndrome of "Anephrexia." In this condition a state of pure retention exists without any of the additional factors which are bound to play their parts in the production of the complete clinical picture when renal function is impaired as the result of disease ("dysnephrexia"). The symptoms may be regarded as due to "urinary poisoning," and they have been constantly reproduced experimentally. "Latent Uraemia" and "Uraemia" should be clearly differentiated, and no attempt made to ascribe them to a common cause such as retention of urinary constituents, as has been done. "Just as hydronephrosis follows an incomplete or intermittent obstruction to the ureters, while atrophy of the kidneys is more likely to follow complete obstruction, so "uraemia" is more apt to follow incomplete failure of excretion, while complete failure produces the syndrome termed "urinaemia." (Langdon Brown).[2.]

In conditions producing "dysnephrexia," however, a certain amount of interference with function and consequent "retention" must exist, and may reasonably be expected to produce symptoms as soon as compensatory mechanisms fail. The symptoms resulting will pre-

sumably be those found in "Anephrexia" - urinary poisoning - though not to such a severe degree. In cases of "uraemia," therefore, two groups of symptoms will exist, (i) those due to the retention of urinary constituents, and (ii) others due to the underlying disease. It is reasonable to assume that those manifestations which are common to both "uraemia" and "Latent uraemia" are due to a common cause viz. urinary poisoning, whilst the remaining symptoms are produced by some unknown factor or factors. That this is a reasonable assumption is supported by the fact that "uraemia" possesses many manifestations not exhibited in "latent uraemia," yet the latter has no symptoms which may not occur in the former.

It is possible to limit still further the number of symptoms which may be described as "uraemic." Many of the symptoms may be due to attempts on the part of the body to find alternative channels of excretion for the retained urinary constituents. This is most probably the case as regards the gastro-intestinal symptoms of nausea, vomiting and diarrhoea. The irritation produced by such vicarious excretion would be sufficient to account for the organic lesions such as ulceration, and catarrhal or diphtheritic colitis sometimes found. This explanation has been held by many for some time past, - von Noorden showed that 8 grammes of nitrogen can be eliminated by the

bowel daily, and 3 grammes by the skin[3] - though it is true that nausea and vomiting may undoubtedly be caused by toxic irritation of the vomiting centre in the medulla. The recent researches of Canti,[4] who found a higher urea content in the vomit than in the blood of the same case, and those of Leiter[5] who found urea to be actively excreted by the stomach, bile and intestine, and in addition was able to produce lesions similar to "uraemic" colitis by these means, strongly support the view that efforts at vicarious excretion play their part in the production of these symptoms.

The skin lesions may similarly be referred to an attempt at alternative elimination. The fact that urea, uric acid and ammonia have all been found in the perspiration in renal disease, and to the most marked degree in cases of "uraemia," is in favour of this view. Langdon Brown[6] has suggested that the pruritis may be caused by the excess of sodium chloride setting up osmotic currents in the lymph between the prickle cells of the skin. The local pareses, and myoclonic movements have been referred by Brelet[7] to a local intoxication of the muscles, and not to a central cause.

Such an hypothesis restricts the term "uraemic syndrome" to the <u>cerebral</u> and <u>respiratory</u> groups of symptoms, but the conditions which may give rise to

any of these symptoms are very variable. Nephritis, using the word in the strict sense, is not an essential precursor of "uraemia." In "toxaemic kidney" the kidney is suffering from tubular degeneration the result of some chemical poison e.g., mercurial salts, arsenic and cantharides, or endogenous poisoning, of which the toxaemia of pregnancy is the outstanding example, jaundice and diabetes mellitus also being not uncommon causes. There are no inflammatory changes in the kidneys. Such a condition may give rise to convulsions and amaurosis, though apparently it never causes paroxysmal dyspnoea. The outstanding biochemical change is not "retention;" the blood-urea, and blood-sugar, which are raised in many forms of nephritis, are low in this condition. The urinary diastase is high, and the protein loss is mainly at the expense of the globulin. Certain "uraemic" symptoms may therefore occur in cases of non-inflammatory lesions of the kidneys characterised not by the retention of toxins, but rather by an undue permeability. Such a kidney is capable of complete recovery. In the epidemic of acute nephritis which occurred during the war, and of which only about 7 per cent. passed into a stage of chronic nephritis (Tremolières and Caussade),[8] "uraemic" symptoms were comparatively uncommon, and Langdon Brown[9] records a series of 166 cases investigated in which the only "uraemic" manifes-

tation was convulsions in 7 cases, all of which recovered. Convulsions may also arise as the result of sepsis throwing sufficient kidney substance out of action.

Cerebral manifestations other than convulsions are most apt to occur when the interstitial tissue is largely affected, and the blood pressure becomes raised. "Uraemic" symptoms may be precipitated in chronic interstitial nephritis by the inability to absorb sufficient water to maintain an adequate blood volume when the kidney is incapable of excreting a concentrated urine, e.g., in cases of new-growth of the oesophagus and stomach.[10.]

Paroxysmal Dyspnoea is most apt to occur in cases of chronic parenchymatous nephritis, in which condition all "uraemic" manifestations are common.

Nephritis is not necessarily followed by "uraemia," and in focal embolic nephritis "uraemic" symptoms are rare at any time; whilst "leaky kidney," a condition in which the kidney has suffered from an earlier but non-progressive lesion, is not associated with any "uraemic" symptoms at all. This state is compatible with normal health and runs a favourable course despite the presence of a large amount of protein in the urine. There is no retention of the urinary constituents.

A very unusual condition in which convulsions

have occurred which have been termed "uraemic," is that of dilated stomach with stenosis of the pylorus. The condition is related to actual "uraemia" for there may be a rise of the blood-urea to figures double the normal, or higher, even when there is no evidence of concomitant renal disease. The connection between pyloric stenosis with gastrectasis and a high blood-urea with "uraemic" symptoms is obscure, but gastro-enterostomy may cause the high concentration of urea in the blood to disappear, and relieve the delirium and other "uraemic" symptoms.[11]

From this brief survey of the conditions under which the manifestations of "uraemia" may arise, it will be observed that certain of the symptoms tend to occur along with each other, with similar conditions, and have other points in common. It thus becomes possible to isolate three groups, (i) Convulsions and Amaurosis, (ii) Paroxysmal Dyspnoea, (iii) Cerebral symptoms apart from convulsions and amaurosis.[12]

(i) Convulsions and Amaurosis, the most dramatic symptoms, tend to occur with the same type of case. They may develop in quite recent cases, and are not common with the more chronic conditions. Either may be the first sign of a kidney lesion, and they may each come on quite suddenly. They have been compared with eclampsia, which may come on very suddenly, and from which recovery may be complete. It is possible

for complete recovery to occur from either convulsions or amaurosis, a statement which cannot be applied to any other "uraemic" manifestation. These points in common between the two symptoms suggest the probability of both being due to the same cause.

(ii) Paroxysmal Dyspnoea appears to have nothing in common with any of the other symptoms, and the suggestions as to its causation may be conveniently described here. There are two important theories held:-

(i) An attempt to compensate for acidaemia.

(ii) The result of changes in the vessels of the respiratory centre in the medulla.

The first theory is based upon (i) the fact that biochemical evidence has definitely demonstrated that an acidaemia is a common feature in nephritis, attributed to the inability of the kidney to excrete acid phosphates, and (ii) the assumption that there is a physiological response in acidaemia to maintain the correct reaction of the blood. Such a mechanism has been clearly demonstrated by Dodds,[13] who studied the normal changes in the alveolar air during the process of digestion. At first, while the acid gastric juice is being secreted the hydrogen-ion concentration in the blood falls, leading to a diminished stimulation of the respiratory centre, and CO_2 tends to accumulate in the alveoli of the lungs. When the alkaline pan-

creatic juice is secreted the hydrogen-ion concentration of the blood rises once more and stimulates the respiratory centre so that CO_2 is washed out of the lungs, and the alveolar air is found to contain less. In health, the kidneys and lungs so co-operate that the hydrogen-ion concentration of the blood is maintained at a fairly constant level, and any alteration is soon compensated for. It is suggested that this co-operation is interfered with in nephritis. The kidney fails to excrete acid sodium phosphate, the hydrogen-ion concentration of the blood must rise, and the respiratory centre is stimulated to compensate for it. The renal incapacity is progressive, and in time the increased respiratory effort becomes manifest, causing obvious dyspnoea. Sometimes, even the marked dyspnoea termed "uraemic asthma" is inadequate to compensate for the acidaemia, which poisons the heart muscle, causing dilatation of the heart and pulmonary oedema, a common clinical finding as the termination of "uraemic asthma."

Under this view, increased ammonia formation is regarded as an attempt to combat the "acidaemia." According to Langdon Brown[14] this is one of the three methods of compensating for acidaemia, of which the other two are hyperpnoea, and increased output of acid in the urine. The last method is interfered with in

nephritis and the two others become inadequate. The occurrence of dyspnoea in paroxysms is explained as due to the temporary diminution of the acidaemia caused by the increased respiratory effort removing more CO_2 from the blood. This is also suggested by the way in which paroxysmal dyspnoea may be replaced by Cheyne-Stokes breathing.

The opposition to this view is based upon the fact that a marked acidaemia is not a constant finding in all cases of "uraemic asthma." Several authorities have recorded cases of paroxysmal dyspnoea in which the plasma reaction was normal or on the alkaline side. Fraser[15] has recently published a series of observations demonstrating this point. Nor is hyperpnoea always strikingly evident in cases of acidaemia, with a plasma bicarbonate of 20 or under.[16] Attention has been drawn to the fact that in those cases in which dyspnoea occurred without an associated acidaemia the blood pressure has always been high, and vascular changes marked, while in some, the renal efficiency was only moderately reduced. It has been suggested, therefore, that the vascular changes may be responsible for the dyspnoea, and cases have been described which showed fibrosis of the arterioles of the medulla oblongata as evidence in support of the view that it is due to impairment of nutrition of the respiratory centre.[17].

The importance of heart failure as a cause of dyspnoea in nephritis must not be forgotten, but such dyspnoea cannot be regarded as true "uraemic asthma."

The most recent biochemical evidence tends to support the view that paroxysmal dyspnoea is due to acidaemia in those cases in which renal efficiency is markedly impaired. It is, however, quite possible for both these theories to be correct. The recent researches of Canti[18] and others, indicate that two groups of cases, both clinically "uraemia," exist. In one the chemical factor predominates, in the other vascular changes are pre-eminent. It is conceivable that in the first group dyspnoea is due to an acidaemia, whilst in the second group, in which impairment of excretion of acid phosphates is insufficient to produce acidaemia, it is due to vascular changes affecting the vessels of the respiratory centre in the medulla oblongata.

(iii) The Cerebral Manifestations other than Convulsions and Amaurosis, such as headache, drowsiness, coma, hemiplegia, insomnia and acute mental changes such as mania or delusional insanity, all have one important feature in common. They tend to occur when vascular changes are marked and the arterial pressure is high. The fact that changes in the blood vessels and high blood pressure are commonly associated with chronic renal disease has long been

known. Of recent years the subject of hypertension has received a good deal of attention, it was thought possible that the same poisons which produced the heightened arterial pressure might be responsible, directly or indirectly, for the "uraemic" symptoms. As yet these poisons are still undetermined. According to O'Connor[19] the relief of the urinary obstruction in patients with high blood-pressure due to prostatic disease regularly reduces the blood pressure, and this suggests that the retention of substances normally excreted in the urine may be responsible. Urea, uric acid and most of the known products of metabolism which are retained do not, however, raise the blood-pressure. It has been stated by Cash[20] that hypertension may be experimentally produced in dogs by the removal of at least 50 per cent. of the renal tissue, if at the same time a portion of devascularised kidney tissue is left inside the body, either procedure alone being ineffective. It is not clear what bearing this observation has upon the occurrence of high blood pressure in chronic nephritis. It was observed by Major and Stephenson[21] that salts of guanidine and methyl-guanidine produce a marked and prolonged rise of the blood-pressure, and as these are substances which are normally excreted in the urine it is suggested that they may be concerned in the production of hypertension in cases of impaired renal function.

That the hypertension is due to the action of a toxin or toxins is supported by the observation by Gheorgian[22] that the blood of patients with hypertension causes a rise in the blood pressure when injected into animals.

Although in cases of chronic interstitial nephritis the blood pressure becomes raised, yet the converse does not always apply, and marked increase in the arterial pressure frequently occurs without any evidence of nephritis, and in these cases, if the heart be sound, the blood chemistry is often normal,[23] though sometimes an increase in the uric acid and cholesterol is found.[24] With hypertension, whether accompanied by evidence of renal disease or not, hyperglycaemia is frequently noted, possibly due to vascular changes in the pancreas.[25]

Substances with a vasoconstrictor action similar to that of adrenaline have been described in the blood,[26] while Hulse has suggested that nephritic blood sensitizes the vessels so that they react more strongly to adrenaline.[27]

While these researches into the cause of hypertension have not been successful, they have produced a great deal of information which has modified the modern conception of chronic renal disease. There is a growing opinion that vascular changes and chronic interstitial changes in the kidneys may not be dependant upon each other, but may be due to the simulta-

neous action of an independent toxin. Batty Shaw[28] has stated that hyperpiesis, a malady in which the blood pressure rises excessively, and "uraemia," may really be the same disease, caused by the circulation in the blood of a poison or poisons which are not due to a fault of the kidney. He has further suggested that the expression "hyperpiesic toxaemia" should be adopted to replace "uraemia."[29] A similar observation has been expressed by Geoffrey Evans,[30] who, as the result of a long series of observations, concluded that the kidneys may be affected by many agents, each one of which is capable of producing an active inflammatory reaction in the tissues attacked, whether epithelial or vascular. If the affection be acute, epithelial reaction dominates the picture; if chronic, epithelial and vascular changes co-exist; if very chronic, only the vessels suffer. Thus, neither vascular nor renal changes can be regarded as the cause of the other, but both are due to the action of some toxic agent. According to Evans diffuse hyperplastic sclerosis is more common in the kidney than in any other organ, and he attributes the recognised association between chronic interstitial nephritis and cerebral haemorrhage to the simultaneous occurrence of similar changes in the vessels of the kidneys and the brain.

The recent researches of Canti[31] on the cerebro-

spinal fluid in "uraemia" have an important bearing upon these opinions. Canti would appear to have differentiated two groups of cases, each of which is clinically "uraemia." In one group a chemical factor can be detected - azotaemia; in the other cardio-vascular conditions, particularly cerebral lesions, are responsible.

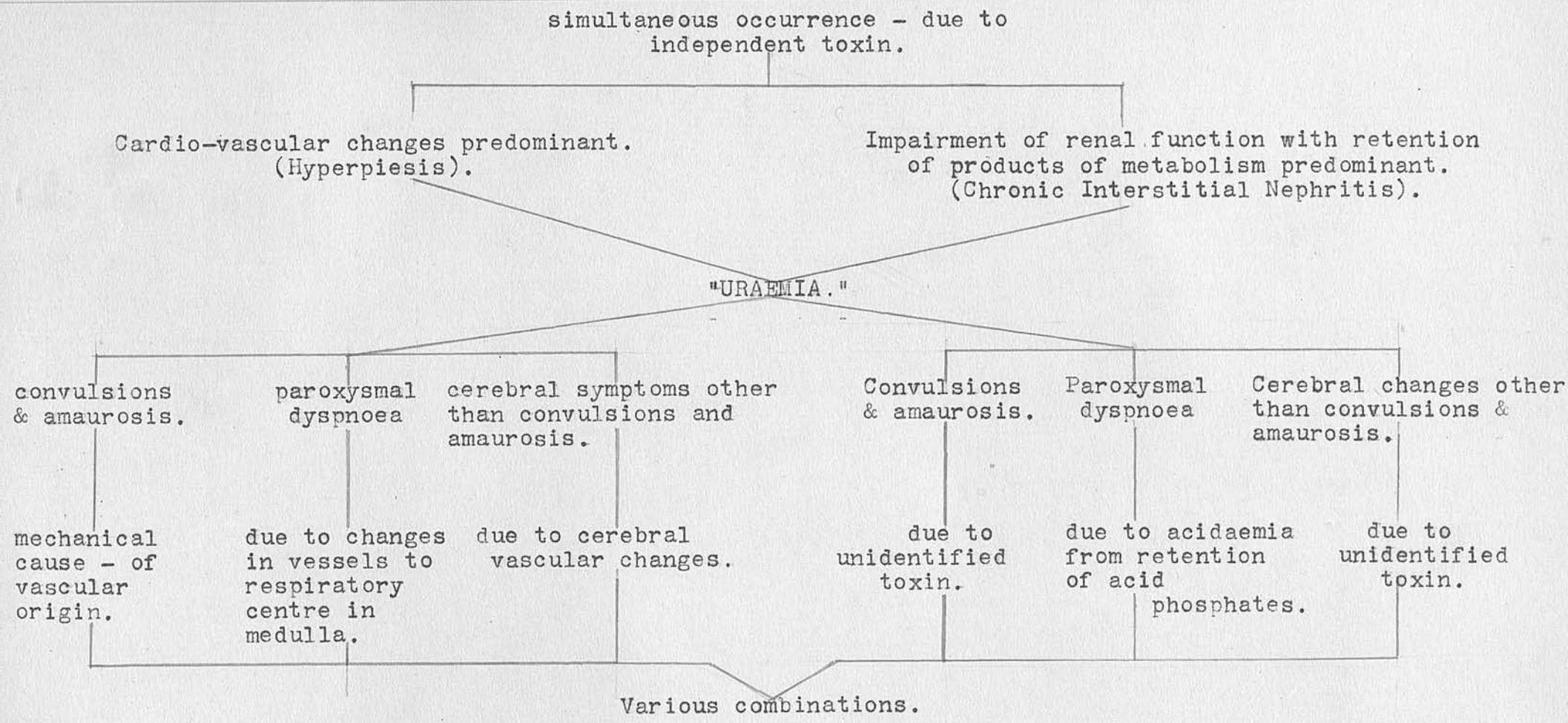
The symptoms of "uraemia" and the conditions under which they occur having been discussed, it is now possible to formulate a conception of "uraemia."

Clinical "uraemia" may occur in two forms; one with a predominant cardio-vascular state and little or no impairment of renal function; the other with impairment of renal function and retention of metabolic products in the blood. The symptoms of "uraemia" are limited to the cerebral and respiratory groups viz., convulsions, amaurosis, paroxysmal dyspnoea and cerebral symptoms other than convulsions and amaurosis. In the cardio-vascular "uraemic" group, the paroxysmal dyspnoea is produced by interference with the nutrition of the respiratory centre by vascular changes: the cerebral symptoms are produced by cerebral lesions of various kinds, vascular in origin. In the chemical "uraemic" group, the paroxysmal dyspnoea is produced by acidaemia caused by the inability to excrete acid sodium phosphates: the convulsions and amaurosis are produced by an unidentified toxin: the other cerebral

manifestations are also caused by toxins which probably differ from that which causes convulsions and amaurosis.

Combinations of the two "uraemic" groups may occur, however, in which case the symptoms may be produced in either way, or both causes may act together.

This conception of "uraemia," and the relationship of hypertension, may be represented schematically as follows:-


simultaneous occurrence - due to independent toxin.
Cardio-vascular changes predominant. (Hyperpiesis).
Impairment of renal function with retention of products of metabolism predominant. (Chronic Interstitial Nephritis).
"URAEMIA."
convulsions & amaurosis.
paroxysmal dyspnoea
cerebral symptoms other than convulsions and amaurosis.
Convulsions & amaurosis.
Paroxysmal dyspnoea
Cerebral changes other than convulsions & amaurosis.
mechanical cause - of vascular origin.
due to changes in vessels to respiratory centre in medulla.
due to cerebral vascular changes.
due to unidentified toxin.
due to acidaemia from retention of acid phosphates.
due to unidentified toxin.
Various combinations.

The causation of all the cerebral symptoms has now to be considered.

The urine unquestionably contains many toxic substances apart from the organic constituents, and, of these, potassium salts are the most potent (Feltz and Ritter).[32] Respiratory symptoms have been attributed to the retention of salts of potassium;[33] while another observer considers potassium chlorate to be the principal cause of vomiting.[34] Potassium salts cannot, however, explain all the urinary toxicity, for the symptoms produced by the injection of urine differ from those produced by potassium salts. It has also been demonstrated that the inorganic ash of urine is less poisonous than the entire urine, and toxic mixtures of organic, ash-free substances have been obtained from normal urine by Dresbach.[35] Few of the known normal constituents of the urine are regarded as toxic to any degree, and these only occur in very small quantities. Urea is regarded as almost non-toxic, uric acid, the purine bases, hippuric acid, creatinine, and the pigments are all possessed of very slight toxicity, and their effects do not explain "uraemia." The old experiments of Bouchard are now largely disregarded on account of the serious errors of technique which they present.

The toxic symptoms of "uraemia" are not, therefore, regarded as due solely or chiefly to the subs-

tances which are normally excreted in the urine, though the symptoms of "latent uraemia" are ascribed to the sum of their effects.

Because the kidney seems to be the chief organ for the removal of the products of nitrogenous metabolism, and the highest figures for non-protein nitrogen are usually found in "uraemia," it might reasonably be supposed that "uraemic" symptoms are due to poisoning by these substances. None, however, have been shown to be capable of producing the symptoms. Also, typical attacks have been observed in which the non-protein nitrogen concentration in the blood has not been high; very high non-protein nitrogen figures in the blood may occur without "uraemia" - Tileston and Comfort[36] found 160 and 159 mg. per cent. in two cases of acute intestinal obstruction, and Foster[37] obtained even higher figures in cases of bichloride of mercury poisoning; none of the known nitrogenous constituents of the urine can be held responsible for all the manifestations of "uraemia." The highest purine, uric acid and creatinine figures in a given case may occur independent of "uraemia;" urea is said to be not sufficiently toxic; and the amino-nitrogen has not been shown to be constantly increased in "uraemia."

The following alternatives may be discussed as representing the views most widely held at the present

time, and as offering the greatest prospect of profitable research.

(i) The nerve cells may be made hypersensitive to some one of the known constituents by the excessive amounts of metabolic products, or by the deficiency in calcium.

(ii) The portion of the unidentified nitrogen usually present in the blood may contain one or more highly efficient toxins.

(iii) Certain mechanical effects.

(i) The first of these suggestions is a speculative hypothesis with, as yet, very little evidence in its support. It has recently been recognised that the normal endothelium of the cerebral vessels is exceedingly impermeable to toxins. Mott[38] has shown, in his study of a case of carbon monoxide poisoning, that multiple extravasations of blood occurred in the brain as the result of fatty degeneration of the capillary endothelium caused by the deprivation of oxygen, and that these lesions were responsible for the later cerebral manifestations. It is suggested that a similar effect may be produced in renal disease; the active inflammatory changes which occur in the cerebral vessels in chronic interstitial nephritis seriously diminishing their impermeability to toxins. The diminished calcium content of the blood is said to make the nerve cells more sensitive to irritants.

(ii) The suggestion that the poisons exist in the "residual nitrogen" is widely favoured at the

present day. That toxins are present in the blood is indubitable. The pathologist recognises evidence of systemic intoxication in "uraemia." The pericarditis, endocarditis and other terminal infections which often fail to yield bacteria are apparently toxic processes. Diphtheritic colitis indicates the vicarious excretion of poisonous substances. Structural changes found in various organs suggest poisoning, e.g., chromatolysis of the cortical ganglion cells, and Lewis' observations of acute parenchymatous and fatty degeneration of the myocardium and the endothelial cells of the liver.[39] The results obtained by the recent electrocardiographic investigations indicate that the heart is under toxic influences. The localised oedemas of nephritis often show a fluid more characteristic of an exudate than of a transudate.

This theory is supported by the evidence that the "residual nitrogen" of the blood tends to be much increased in "uraemia," and also by the recent discoveries of Canti[40] that the non-protein nitrogen of the cerebro-spinal fluid is frequently excessive, and of Brun[41] that the "residual nitrogen" of the cerebro-spinal fluid may be very much increased. It is also supported by the observations of Woods,[42] who found, in a series of cases, that the proportion of non-protein nitrogen of the blood that could not be accounted for

by the known products of nitrogenous metabolism seemed to vary directly with the severity of the symptoms. The investigations of Harrison and Hewitt[43] and others regarding Andrewes' Diazo reaction also favour this theory. The reaction was shown to be specific for "uraemia," and while it was found that nitrogenous retention always accompanies retention of the substance responsible for the reaction, urea retention and Andrewes' test do not run strictly in parallel. Andrewes had previously excluded urea, uric acid creatinin and proteins as the cause of the reaction.

The identity of the poison or poisons is still a matter of conjecture. It has been suggested that they are the more toxic precursors or derivatives of the nitrogenous constituents of the urine. Urea is the final product of a long series of reactions by which the large protein molecule is broken up into its "building-stones," the various amino-acids. Of these, only Arginine splits off urea directly from its molecule. The others are further decomposed in such a way that their NH_2 groups are combined with carbonic acid and excreted as the compound known as urea - $O = C(NH_2)_2$. The immediate precursor of urea is ammonium carbamate, from which it can be formed by simple dehydration. It is known that the liver is able to convert amino-acids to urea, for it has been

shown experimentally that if leucine and glycine are passed through the vessels of the isolated liver they disappear in part, while an increased amount of urea escapes from the hepatic veins. The liver is believed to be the most important site of the formation of urea, though it is also probable that it can be formed elsewhere, but the all-important steps by which urea is produced from the amino-acids are not known. Amino-acids may be broken down by a process of deamination, setting free the NH_2 groups to form urea, or decarboxylation, which produces amines, many of which are toxic. The extent to which such toxic amines occur in either normal or abnormal protein metabolism is not yet known, for, normally, they are immediately or very rapidly destroyed, and are, therefore, difficult to trace in the living body. Some amines have occasionally been found in the urine, e.g., putrescine and cadaverine in cystinuria.

It has, therefore, been suggested that hepatic insufficiency would lead to the circulation of poisonous substances which may cause symptoms of "uraemia," but there is little actual evidence in support of this view. In eclampsia and acute yellow atrophy of the liver, in both of which diseases there is extensive destruction of the liver cells, it is conceivable that the toxic symptoms might be so produced, but in "uraemia" definite extensive changes in the liver are unusual. Nor is this view supported by the recent

researches of Hermannsdorfer,[44] who, in his final experiment, having demonstrated the presence of a convulsive poison in the urine of coelostomized rats, sought to determine whether it owed its origin to derangement of the general metabolism, or whether the kidneys were especially implicated in its production; his results clearly indicating that the kidneys played some part in the production of the poison.

Of the amines which have been suggested as likely to cause "uraemic" symptoms one of the first was Choline, a product of the decomposition of lecithin. Donath[45] found that choline injected directly into the cerebral cortex or under the dura is extremely toxic, causing severe tonic and clonic convulsions. Normal urine contains no choline, or, at most, only a trace. Shanks[46] found that even after feeding large quantities (1 to 2 grammes per kilo,) to rats, none could be recovered from the urine. It is possible that choline is liberated from nerve tissues when they break down in the body during life, but although some observers have claimed its discovery in the blood and cerebro-spinal fluid under certain circumstances, it is probable that these observations depended upon faulty methods of analysis, and it is very doubtful if enough choline is ever set free at any time to be detected by chemical means. Hunt[47] devised a test which enabled as little as 0.00001 mg. to be detected,

but was unable to obtain any evidence that choline is of any significance in either physiological or pathological processes. Guggenheim and Löffler[48] found the equivalent of from 2 to 20 mg. per litre in blood-serum, and about the same proportion in the urine, there being no characteristic variations in disease. Choline is only possessed of a feeble toxicity, its action being similar to the allied and much more potent substance neurine; it lowers the blood-pressure, and is not sufficiently toxic, in the quantities present in the blood, to account for the symptoms of "uraemia."

Although choline is feebly toxic, yet from it may be formed a highly toxic body acetyl-choline. There is no evidence that this substance is produced from choline in the body, but in view of the enormous toxicity of this choline derivative there must always be considered the possibility that such toxic compounds may at times develop in amounts too small to be detected, but large enough to cause effects. (Wells).[49]

Another substance which possibly owes its presence in normal blood and cerebro-spinal fluid to the decomposition of lecithin is Trimethylamine. This substance has been found to be increased ten-fold in the blood and cerebro-spinal fluid in cases of "uraemia," but is not increased in cases of "latent uraemia," in which convulsions are absent.[50] According to Golla

it is very highly toxic and reproduces convulsions experimentally, and he is inclined to attribute the whole of the "uraemic syndrome" to this poison. This important observation awaits development.

Among the substances which may be derived from the amino-acids of proteins by the process of decarboxylation (loss of CO_2) are the so-called Pressor Bases. These amines, of which the most important are tyramine and histamine, are possessed of marked power to stimulate the sympathetic nervous system. Tyramine raises the blood-pressure and slows the pulse rate, its action being similar to that of adrenalin, which however, is much more potent. Histamine does not raise the blood-pressure although it constricts the peripheral vessels. Such pressor substances have been suggested as the cause of hypertension, as has already been stated. The importance of such bases in "uraemia" is indicated by the recent researches of Foster,[51] who has isolated a toxic base from the blood of "uraemics" capable of causing convulsions. Hewitt,[52] in 1924, after conducting a series of observations on Andrewes' Diazo colour reaction in "uraemia," made the suggestion that the substance responsible for the reaction might be a cyclic amine similar to tyramine, or histamine. It is conceivable that Foster's "toxic base" may be the substance responsible for Andrewes' reaction.

This theory is further supported by the recent researches of Hartman,[53] already referred to, who claimed to have isolated the substance "urinod" from the urine of "uraemics," which causes mental symptoms, but this important observation awaits conformation.

It would appear, therefore, that there is a considerable weight of evidence in favour of the view that the portion of the unidentified non-protein nitrogen of the blood does, in "uraemia," contain poisons, as yet unidentified, which are quite capable of producing the symptoms of "uraemia." There is not yet sufficient evidence in favour of any one of the suggested substances, and recent researches suggest that there may be several.

Before terminating this account of the probable toxins of "uraemia" it is necessary, in view of recent researches, to draw attention to the facts that, despite the prevailing opinion to the contrary, it is quite possible for the manifestations of "uraemia" to be caused, in certain cases, by the known nitrogenous substances which the kidneys have been unable to excrete, and that investigators have failed to take into account the "time factor" of chronic disease. The experiments of Leiter,[54] and of Hewlett, Gilbert and Wickett,[55] suggest that urea retention cannot be entirely excluded as a factor in the causation of "uraemic" manifestations if the "time element" be

taken into consideration. Becher, also, has recently supported this view.[56] Further experiments along the lines used by these investigators are required to discover what effects are produced not only from urea, but from creatinine, and uric acid, when kept in the blood for long periods at the concentrations found in "uraemia," as well as from any other substance that may be increased in the blood in "uraemia."

(iii) The nervous symptoms of "uraemia" are often distinctly focal, and a complete hemiplegia from haemorrhage may be exactly simulated, or seizures identical with those of brain tumour may be seen. Some continental writers[57] hold the view that a true "uraemic" picture may occur due solely to cerebral oedema from salt and water retention. It occurs especially in the young, and is to be distinguished from the "uraemia" of nitrogenous retention, and from a pseudo-uraemia resulting from arterio-sclerosis. In the "cardio-vascular uraemic group" the symptoms have a vascular origin, but in the "chemical uraemic group" also, they may be due to a mechanical cause, and their occurrence may indicate a combination of the two groups, for it is extremely difficult to explain these localisations by the action of a soluble poison, and simple if a local oedema be assumed. Although it is also difficult to explain the localisation of such oedema, yet it is known that localised oedemas

do occur in nephritis, which fact provides a basis for the assumption of the occurrence of localised oedema of the brain. Fischer's suggestion that a localised acidosis may be the cause of localised oedema has already been described[58], but there is no evidence in support of his view. It has also been suggested, in view of the high osmotic pressure of the blood in "uraemia," and the fact that the life of nephrectomised rabbits may be prolonged by giving them water (Couvee)[59], that osmotic effects may be responsible for local oedemas. As the existing evidence is not sufficient to explain the symptoms on a solely toxicological basis, the alternative explanation of cerebral oedema must be taken into consideration. Nor is it sufficient to say, as was said of Traube's original theory, that oedema or other gross lesion of the brain is not a constant post-mortem finding, nor that such an hypothesis could not explain all the symptoms, for, as it is now realised that "uraemic" symptoms may have many different causes, there seems to be no adequate reason why, under certain circumstances, cerebral oedema should not be one of them.

Parkes Weber[60] has recently drawn attention to the apparently mechanical factor which may cause "uraemic" convulsions in certain cases. He described cases of young adult patients which were occasionally seen, with acute renal dropsy lasting for months,

requiring repeated drainage of ascites, hydrothorax and oedema of the legs, and apparently "hopeless cases of large white kidney." Eventually the oedema would entirely disappear as the result of a "diuretic crisis," although albuminuria persisted. Some of such cases, but not all, were connected with early syphilis. Vomiting and headache were occasionally present, but one of the greatest dangers was the onset of "uraemic" convulsions, which in this class of case was likely to be followed by death. "It seemed as if the uraemic convulsions in such cases, when they occurred, were due to a kind of overflow of the dropsical effusions from the subcutaneous tissues, peritoneum and pleurae, into the cerebro-spinal system, thus giving rise to excess of cerebro-spinal fluid (and possibly to oedema of the meninges and brain itself) and cerebral anaemia by compression of the brain." Volhard has also recently subscribed to this view.[61]

A mechanical factor is introduced in the recent suggestion of von Monakow[62] that the suddenness with which "uraemia" develops may be explained as being due to yielding of the choroid plexus. So long as the choroid plexus is normal it serves as a protecting membrane to ward off toxic fluid from the brain, but when it becomes abnormally permeable, the brain is flooded with the poisonous substances circulating in

the blood stream. He has found fibroid and other changes in the choroid plexus after death from "uraemic" coma.

A mechanical hypothesis is advanced by Ervin[63] who maintains that convulsions occur when the blood pressure becomes lower than the intracranial pressure, so that the blood supply of the brain is reduced; the convulsion raises the blood pressure. He comments upon the difficulty of explaining the transient character of uraemic convulsions if caused by concentrated chemical poisons.

There is very little real evidence in support of any of these suggestions except the occasional finding of "wet-brain" on post-mortem examination, or the even rarer occurrence of grosser vascular lesions. Nordman[64] has found the characteristic lesions of chronic meningitis in "chronic uraemia." There is, however, considerable presumptive evidence in favour of the view that a mechanical factor may be the cause of "uraemic" symptoms in certain cases.

In order to make this survey complete, I propose to describe two other theories of the causation of "uraemia" which cannot be included under any of the previous headings. These suggestions, (i) the doctrine of the internal secretion of the kidney, and (ii) the allied theory of nephrolysins and nephrotoxins, have little evidence to support them, and by

the majority of authorities are not seriously considered at the present time, but, as the possibilities of the theories have never been entirely disproved, however, and some workers still hold these views, they cannot be regarded as wholly obsolete.

(i) The possible influence of an Internal Secretion of the Kidney was first advanced by Brown-Séquard[65] in 1892. It was further supported in 1897 by the experiments of Ajello and Paraveandalo,[66] and of Rose Bradford.[67] The last named worker concluded that the kidney had an internal secretion which regulated nitrogenous katabolism which in its absence went on unchecked. Rose Bradford's experiments and conclusions were criticised by Beddard and Bainbridge,[68] however, who found that the increased output of urea occurred only as a terminal event when the animal experimented upon was so ill that it was unable to take food and was starving, and it has long been known that after prolonged starvation, there is, for some time, a rise of urea excretion due to the animal living on its tissue protein alone.

Ascoli[69] conducted a series of experiments in support of Brown-Séquard's view and confirmed the fact that dogs die sooner after bilateral nephrectomy than after ligation of the ureters. In both cases the retention of extractives is the same, but in cases in which the kidneys have been excised there is, in

addition, loss of any internal secretion. It was found that if such a possible secretion were replaced by an injection of renal juice or of normal serum into animals after nephrectomy, they lived as long, or even longer, than the animals with both ureters ligated. After such injections normal respiration was re-established, even in animals who had passed into a state of coma and Cheyne-Stokes breathing. (Meyer).[70]

In 1907, von Noorden[71] reviewed the evidence and stated that "so far, very little reliable material is forthcoming, and the question has not advanced beyond the hypothetical position of Brown-Séquard." It has been discovered, however, and confirmed by many workers that renal juice contains a substance which raises the blood-pressure (Meyer, Ascoli and Figari, Levon, Tigerstedt and Bergmann, Riva-Rocci).[72]

In 1908, and again in 1910, Pearce[73] after carefully reviewing the suggestion, found no evidence that an internal secretion of the kidney was an influential factor in the production of "uraemia." A similar opinion has been expressed by most later workers, though the majority are agreed that extract of kidney cortex contains a substance capable of raising the blood-pressure.[74].

In Hermannsdorfer's recent work, the second experiment was especially devised to retain, and make

use of, any internal secretion that might be formed by the kidneys. The results of this experiments showed definitely "that the kidney has no antitoxic endocrine function in relation to uraemia."[75].

(ii) The theory that "uraemia" might be due to the Products of Nephrolysis is associated with the name of Ascoli.[76] It was claimed that if one kidney be destroyed by ligation of its vessels or ureter, the other kidney will develop serious degenerative changes, but that this will not occur if the first kidney be entirely removed. These changes were attributed to the action of nephrotoxic substances which are produced in reaction to the absorption of the injured renal tissue that has been left in the body. Other methods of renal injury have been thought to produce similar effects, and the serum of animals with kidney disease was said to injure the kidneys of normal animals.[77] Upon this basis an attempt was made by Kapsenberg[78] to explain the progressive nature of the chronic nephritides as being the result of nephrotoxins produced following the absorption of the injured cells, which nephrotoxins injure still other renal cells. Such a process, however, would necessitate the production of cell toxins in an animal which are toxic for its own cells, that is, autocytotoxins. It has been found, however, to be very difficult to produce autolysins of any kind, and there is no reason

to expect the kidney to be an exception. Pearce[79] conducted experiments, but was unable to produce any isonephrotoxins, and could not corroborate the changes said to have been found in the remaining kidney after ligation of the vessels of the other. He succeeded, however, in obtaining an active heteronephrolysin, but also found that immunisation with liver produced nearly as active nephrolytic serum as did immunisation with kidney. Fleischer[80] has recently demonstrated that antikidney serum does react specifically with at least some of the antigens of kidney tissue.

Numerous attempts have been made to obtain serum toxic for various tissues, with varying success. In general, it can be said that it has <u>not</u> been found possible in this way to throw out of function one particular organ.[81] It may be said, however, that recent developments indicate that various tissues not only contain proteins which exhibit the characteristics of the entire animal, but also other proteins or antigenic radicals which are more or less independent of these, and characteristic to a certain degree for the tissue from which the antigen was obtained. Thus, Hektoen and Schulhof[82] have obtained specific precipitins for the proteins of the alimentary mucosa distinguishing them from the serum proteins; and Fleischer's experiments have shown the presence of both specific and common antigens in organ extracts.

The problem of specific cytotoxins cannot therefore be considered as finally closed; improved methods for separating antigens may result in the production of antibodies for a single tissue or organ.

One may conclude, therefore, that in respect of these two theories there is no reliable evidence in support of either. It has not been proved that the kidney produces an internal secretion, and this must be done before its association with "uraemia" is assumed. It is, however, generally accepted that expressed renal juice contains a substance with a pressor effect similar to that of adrenaline and pituitrin. In the case of the theory of nephrolysins, although the subject of the formation of auto-cytotoxins may eventually prove of general importance, there is no present evidence that justifies its association in any way with the production of "uraemia."

C O N C L U S I O N.

Having endeavoured to fulfil the intention expressed in the Introduction to collect, and to give a complete and orderly description of all that is of importance in the work and conclusions of investigators on the subject of "uraemia" from its earliest days up to the present time, and also to discuss the modern theories in the light of recent researches with a view to indicating in which direction future investigation is most likely to prove profitable, I propose, in conclusion, to recapitulate concisely the main opinions expressed in the course of the Thesis.

1. The terms "Uraemia" and "Latent Uraemia" should be discarded, and, as at present conceived, there is no necessity for the continued description of "uraemia" as a separate entity.

2. "Anephrexia" is suggested as a name for the syndrome which may occur as the result of suppression of urine unassociated with active disease of the kidneys. The symptoms are due to the retention in the body of the substances normally excreted in the urine - "urinary poisoning."

3. "Dysnephrexia" is suggested as a term to indicate the state of the kidneys in all conditions, whether primarily renal or not, in which their excretory functions are impaired, but in which the disabi-

lity is only partial. This state and that of "Anephrexia" should be clearly differentiated, and no attempt should be made to attribute them to a common cause.

4, Many of the described symptoms of "uraemia" may be explained as being due to efforts at vicarious excretion. The "uraemic syndrome" may be restricted to the Cerebral and Respiratory groups of symptoms.

5. General vascular changes and chronic renal disease, probably the result of the simultaneous action of a toxin, occur concurrently, though not to the same degree. Clinical "uraemia" may thus occur in two forms. In the first form, cardio-vascular changes are marked and renal function is but little impaired; the acute cerebral symptoms are due to mechanical causes of vascular origin, the chronic symptoms to changes in the cerebral vessels, and the paroxysmal dyspnoea to changes in the vessels of the respiratory centre in the medulla oblongata. In the second form, impairment of renal function is predominant; the cerebral symptoms are due to unidentified toxins, and the paroxysmal dyspnoea to acidaemia; as vascular change is also present this may be an additional factor.

6. The residual nitrogen of the blood in "uraemia" contains toxic products of abnormal metabo-

lism capable of producing "uraemic" symptoms, although none of the suggested substances can be regarded as the specific toxin of "uraemia." The liver may be concerned in the production of these toxins but their origin cannot be entirely attributed to hepatic insufficiency.

7. It would appear to be quite possible for the manifestations of "uraemia" to be produced, in certain cases, by the known nitrogenous substances which the kidneys have failed to excrete. Further investigations are required as to the effects of substances maintained in the blood for long periods at the concentrations found in "uraemia."

8. There is no reason to suppose that either the loss of an hypothetical internal secretion of the kidney, or the production of nephrolysins, is in any way concerned in the causation of "uraemia."

9. In view of the varied symptomatology of "uraemia," it is highly probable that several causes may act in combination. In one case there may be a toxic factor, which in another may be complicated by the effects of acidaemia or of high blood pressure; the diminished calcium content of the blood may increase the excitability of the nerve cells, or the retained products of metabolism may reduce the impermeability of the cerebral vessels to toxins. All possible variations of co-operating influences may be expected to occur in the varied circumstances which lead to the "uraemic state."

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